THE PATHOLOGY OF HEART VALVE REPLACEMENT BY VALVULAR PROSTHESES

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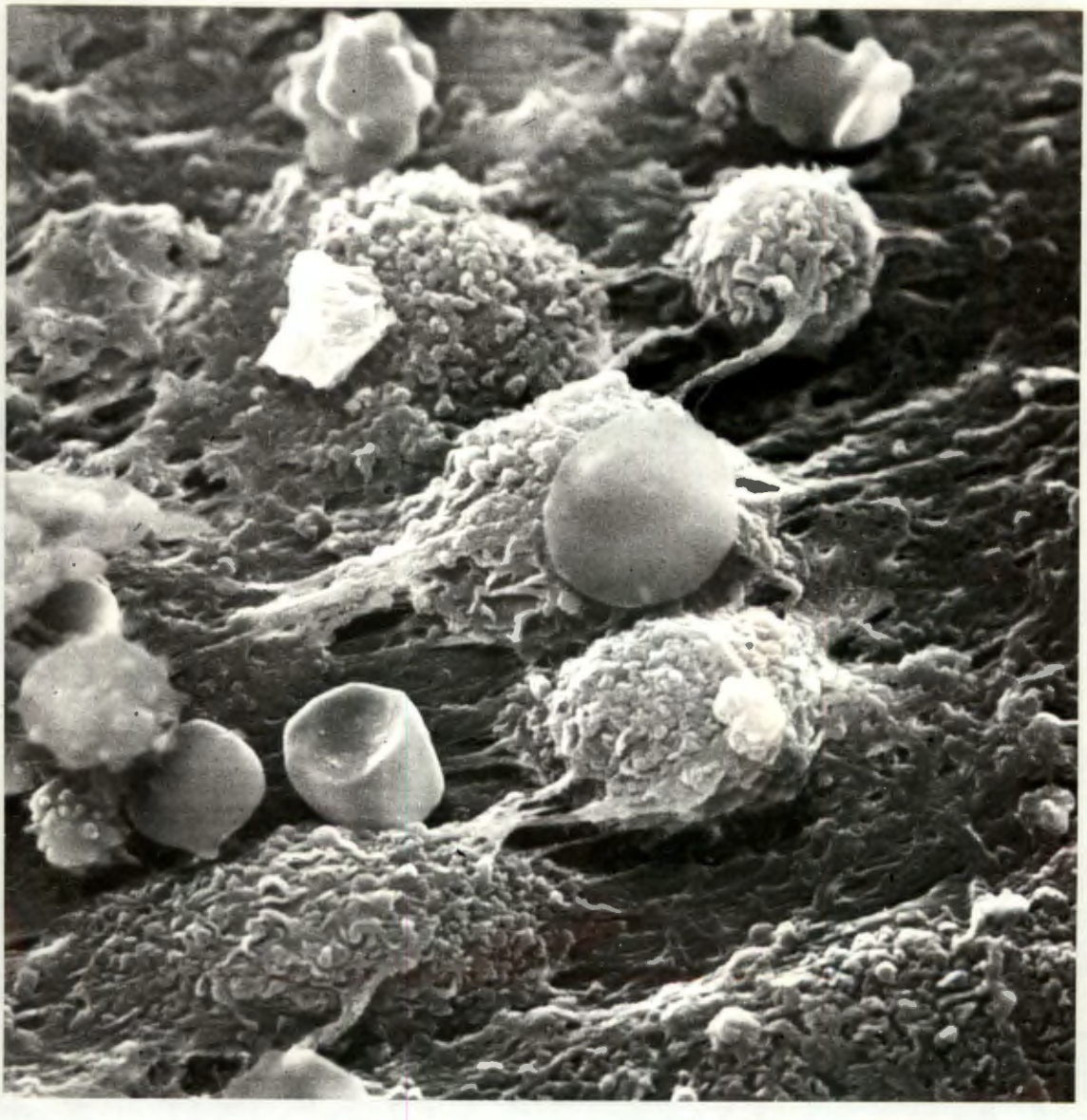
FOR MY PARENTS, WIFE AND CHILDREN



FRONTISPIECE

Scanning electron microscopy of a Mitroflow bovine pericardial heart valve, which had been implanted in a baboon for 36 days. Mesothelial covering cells have been lost exposing bare collagen, which is partially covered by histiocytes (cells with ruffled cytoplasmic processes), erythrocytes (some of which are crenated) and scanty fibrin. (Uranyl acetate & lead citrate, X 4000).

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STATEMENT OF CANDIDATE

I declare that the work on which this thesis is based is original (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other University.

ACKNOWLEDGEMENTS

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Mr S. Isaacs, statistician in the Department of Medical Informatics, Groote Schuur Hospital gave advice on the statistical methods used in this work. Mrs M. Stansfield created the line drawings of the mechanical and tissue valves.

ABSTRACT

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This study reviews the pathological findings and principal causes of death in 290 patients with 360 implanted heart valve prostheses. It is preceded by a survey of the dramatic history of the development of cardiac valve surgery, which spans the relatively short period from 1896 to the present time. The autopsy incidence of various forms of valvular heart disease as reflected in the autopsy records of the University of Cape Town Department of Pathology is also reviewed. Acquired valvular heart disease was encountered in 6.8% of 18,132 autopsies performed over a 30-year period (and most often involved the mitral valve). Congenital heart disease was encountered in 2% of the same group of autopsy patients. The clinical indications for heart valve replacement and trends in cardiac surgery at the University of Cape Town are briefly reviewed.

Retrospective analysis of the pathology of 100 consecutively replaced natural heart valves in conjunction with the operation notes and the information given to the original examining pathologist revealed that the most helpful information for the pathologist is that which is contained in the operation notes and pertains to the appearance of the valve prior to excision. This is especially so in the case of the aortic valve, which is usually removed as multiple fragments. Aschoff bodies were encountered in 10.3% of surgically removed atrial appendages (and in 11.3% of of those removed from patients suspected of having rheumatic valvular disease). About 25% of atrial appendages removed from patients with mitral stenosis showed positive Aschoff bodies. Only 0.9% of autopsy patients with implanted cardiac valve prostheses showed Aschoff bodies. Rheumatic fever was the underlying disease leading to cardiac valve replacement in 73% of all patients with implanted valvular prostheses in this autopsy series.

ABSTRACT

Design criteria for the ideal heart valve substitute are summarized and most of the commercially available heart valve prostheses are classified and their structure described. An approach to the identification of heart valve prostheses by macroscopical examination and radiological means is also given.

The body of the thesis details the pathology and principal causes of death in each of the different types of mechanical and tissue valves that have been used at Groote Schuur Hospital, Cape Town. These valves include the University of Cape Town prosthesis, Starr-Edwards ball-valve, Bjork-Shiley tilting-disc prosthesis, Lillehei-Kaster pivoting-disc valve, St Jude Medical valve, the University of Cape Town formaldehyde-preserved xenograft porcine aortic valve, the Hancock prosthesis, and the Carpentier-Edwards valve. Details of limited experience with autologous fascia lata and Ionescu-Shiley prostheses are also given. Patients with mixed (more than one type of valve prosthesis) in the same heart are dealt with as a separate group, as are valve prostheses situated within tube grafts.

Miscellaneous aspects of the pathology of valve replacement examined include the cardiac conduction system, renal haemosiderosis, subvalvular aneurysm complicating mitral valve replacement, the state of the major and small coronary arteries and the myocardium ; the post-perfusion pulmonary syndrome and pancreatic changes related to heart failure. Conduction system haemorrhage is commonly associated with heart valve replacement, and may be related to relative hypoxia during bypass rather than direct surgical trauma. Significant renal haemosiderosis was observed in 25% of patients with valvular prostheses and was confined to the mechanical prosthetic group only. None of the patients had gallstones. Excessive excision of a (calcified) mitral ring may lead to loss of atrioventricular continuity and development of a sub-epicardial haematoma. The latter may be complicated either by external rupture or formation of a false

aneurysm.

Patients with post-operative myocardial failure had significantly heavier hearts than those without failure. Myocardial necrosis was more severe in patients with implanted valvular prostheses compared to non-operated controls. For some unexplained reason patients with Starr-Edwards prostheses showed significantly more necrosis compared to patients with other types of prostheses. No significant difference in necrosis scores was noted between the following categories of patients : (i) two groups of patients with different types of myocardial protection (intermittent coronary perfusion with a beating heart versus cold cardioplegic cardiac arrest) during cardiopulmonary bypass ; (ii) intermittent versus continuous coronary arterial perfusion with blood during bypass ; (iii) regularly beating hearts versus those hearts which fibrillated during bypass ; (iv) early (less than one month) surviving patients compared to those that died later.

Although the hearts of most patients showed some histological evidence of fibrosis, naked eye examination revealed sub-endocardial fibrosis in only 8% of the operated patients and trans-mural fibrosis in 3%. Morphometry (point-counting) revealed no significant difference in the amounts of myocardial fibrosis in patients with prostheses compared to non-operated controls. Assessment of fibrosis using a more subjective morphological scoring system showed higher scores for replacement and interstitial fibrosis in patient with prostheses compared to controls and replacement fibrosis was more common in the longer surviving operated patients. Morphometrical assessment of fibrosis in functional classes of valvular dysfunction showed that patients with pre-operative aortic incompetence or mixed aortic valvular disease yielded higher fibrosis scores than controls with similar valvular dysfunction. The general conclusion from the present study is that overall patients with implanted valvular prostheses show a similar degree of myocardial fibrosis to that seen in non-operated controls with valvular disease.

ABSTRACT

Comparison of results in the different types of valves showed that the tissue valves bore significantly fewer thrombi and that, in general, the thrombus was much scantier in amount than that observed on the mechanical prostheses. These two groups of valves showed no significant difference with regard to infarcts of systemic organs. Patients with prostheses showed infarcts of the spleen, brain and heart more often than did non-operated controls with (predominantly) rheumatic valvular disease. Renal infarcts were just as frequently seen in the control patients, who also showed a higher incidence of pulmonary infarcts. Amongst the mechanical valves, patients with Starr-Edwards valves showed the greatest incidence of fatal thromboembolism. Prosthesis-related problems formed the biggest single principal cause of death in all patients with valve prostheses. This was because the mechanical valve group, which comprised 82% of the total, had prosthesis-related problems as the prime cause of death. In the tissue valve group this complication ranked third in importance after unknown causes and diseases unrelated to valve surgery. Analysis of the valve-related causes of death showed that thrombosis and infection of the prosthesis were more important in the mechanical valves, whereas structural failure was more common with the tissue valves. The University of Cape Town valve, the Lillehei-Kaster valve, and the Starr-Edwards valve had the highest incidence of prosthesis-related complications, whilst the Bjork-Shiley, Carpentier-Edwards, Hancock and St Jude Medical valve prostheses gave better results in this regard. Examination of the total group of autopsy patients with valvular prostheses revealed that prosthesis-related fatal complications were present in 13% of the patients who died within 30 days post-operatively, and in 61% of those who died later.

Creation of the ideal heart valve substitute is still a long way off, and even the most modern "state-of-the-art" prosthetic valve e.g., the St Jude Medical mechanical valve is still greatly dependent upon continuous anticoagulation for

its adequate function. Experimental evaluation in baboons of a newly developed bovine pericardial (Mitroflow) valve showed no significant advantage over another similar commercially available valve. Over the short period of evaluation, thrombosis and host tissue overgrowth were significant complications. Unlike the overall development of cardiac surgery, which has made dramatic advances about once every 5 years, improvements in the design and function of prosthetic heart valves seems to occur as a steady slow march with occasional halts and diversions into cul-de-sacs.

INTRODUCTION

INTRODUCTION

The human heart is a unique pump system which, using a few watts of power, circulates nearly 3 million litres of blood through the body of an average-sized adult each year(1). The efficiency of a well-functioning heart depends upon the adequate function of the heart valves and thus advanced valvular heart disease may severely disable the heart's pumping capacity and lead eventually to death. Cardiac valve replacement aims to restore the circulatory haemodynamics to normal, or to as near normal as possible. The need for heart valve replacement is clearly established. Nevertheless, there is often considerable uncertainty regarding the optimal timing for surgery, the appropriate prosthesis to use,and the ultimate prognosis for the individual patient(2).

Many varieties of prosthetic valves have been used in clinical practice, but recently tilting disc valves and xenografts have been more commonly used. However, no prosthetic valve as perfect as the normal human heart valve has yet been developed. Replacement valves, although generally helpful in returning patients to normal life, may also cause significant complications. Many serious problems associated with heart valve replacement remain unsolved. According to Hwang et al.(1) the prominent problem areas are: (i)thrombus formation and thromboembolism, (ii)damage to the blood elements by mechanical stress, (iii)damage to the endothelial lining by mechanical stress, (iv)tissue overgrowth, (v)mechanical failure due to fatigue or chemical change in the valve materials, (vi)biochemical reactions, (vii)suture tearing, and (viii)infections. In addition to continuous clinical evaluation of heart valve prostheses, the solution to most of these problems will depend on inter-disciplinary contributions from biomedical engineering, material science, biochemistry, pathology and related fields. Whilst there is a plethora of reports detailing the clinical and haemodynamic effects of various prosthetic heart valves, there are far

fewer articles describing the cardiac pathology and general autopsy findings in patients who have died following implantation of such prostheses. Despite the fact that more than 30,000 patients in the United States of America alone undergo this procedure each year, few studies have analysed the autopsy-determined causes of death in a large population of such patients(3).

Research and development for newer and better prosthetic valves is being actively undertaken(4). However, the ultimate evaluation of a replacement heart valve can only be obtained from patients with implants. Clear identification of fatal complications following heart valve replacement is of the greatest importance in planning means of lowering the post-operative mortality rate. Autopsy evaluation of a patient's cause of death is more accurate than a solely clinical assessment(5-7). If an autopsy has been performed, one has substantial evidence as to whether or not the death was valve related(8).

The main aim of the present study is to determine the principal causes of death in all patients with heart valve prostheses who were autopsied in the University of Cape Town Department of Pathology from the beginning of 1962 up to the end of 1982. In some cases, possibly more than one explanation of the cause of death was valid, but a judgement was made as to which factor appeared to be the dominant cause. Although there may be some disagreement regarding a particular patient's principal cause of death, as long as the same person is making the judgement, the information is useful in comparing one prosthesis, or one patient with a prosthesis, with another(9). Other associated aetiological factors favouring a fatal outcome were also examined. In addition to the autopsied patients, information obtained from surgically excised heart valves and from experimentally implanted prostheses was also analysed.

The thesis is arranged so that following on the methodology, historical review, and a description of the

various types of prosthetic heart valves, the pathology of each type of prosthesis implanted in patients at Groote Schuur Hospital is dealt with separately. Certain pathological conditions common to all of the patients are examined in Chapter 17. Chapter 18 reviews the pathological findings in all of the autopsied patients with prosthetic heart valves.

DEFINITIONS, ABBREVIATIONS AND SYMBOLS

DEFINITION OF TERMS

POPPET (BOBBIN,OCCLUDER) is the mobile portion of the prosthesis which seals the prosthetic orifice. It may take the form of a ball, disc or leaflet.

BASE RING is the circular structure in the plane of the valve annulus, which in the case of mechanical prostheses supports the cage, and which supports the stent of xenograft prostheses.

SEWING RING is that portion of the valve through which sutures are passed to tether the prosthesis in the native valve ring. The sewing ring surrounds, and is attached to, the base ring.

CAGE is that portion of a mechanical prosthesis which, in conjunction with the base ring, limits the excursion of the ball, disc or leaflet.

The cage is composed of STRUTS which join the cage to the base ring. If all the struts emerge on one side of the base ring plane, the cage is SINGLE. If the struts emerge on both sides of the base ring plane, the cage is DOUBLE. If converging struts are not connected, the cage is OPEN ; otherwise the cage is CLOSED.

STENT is the supporting structural framework of a tissue valve. It arises at a right angle to the base ring of a xenograft prosthesis and supports the valve leaflets.

AORTIC NODULAR SCLEROSIS is an alternative term for SENILE TRICUSPID ACQUIRED CALCIFIC AORTIC VALVE STENOSIS.

ABBREVIATIONS AND SYMBOLS

AS=AORTIC STENOSIS
AI=AORTIC INCOMPETENCE
AV=AORTIC VALVE
AVN=ATRIO-VENTRICULAR NODE
AVR=AORTIC VALVE REPLACEMENT
BH=BUNDLE OF HIS
B-S=BJORK-SHILEY
CABG=CORONARY ARTERIAL BYPASS GRAFT (USING SAPHENOUS VEIN)
C-E=CARPENTIER-EDWARDS
CM=CARDIOMYOPATHY
cm=CENTIMETRE
cm2=SQUARE CENTIMETRE
COMM=COMMISSURAL
CUMUL.=CUMULATIVE
Ed.=Editor
ERYTH=ERYTHEMATOSUS
et al.=ET ALIA:'AND OTHERS'
GPVs=GLUTARALDEHYDE PRESERVED PORCINE AORTIC VALVES
e.g.=EXEMPLI GRATIA:'FOR EXAMPLE'
g=GRAM
HAN=HANCOCK
HUFN=HUFNAGEL
Hg=MERCURY
i.e.=ID EST:'THAT IS'
I-S=IONESCU-SHILEY
LBB=LEFT BUNDLE BRANCH
LILL=LILLEHEI
LUETIC=SYPHILITIC
mm.=MILLIMETRE
M=MUSCLE
MI=MITRAL INCOMPETENCE
MIXED PROSTHESES=MORE THAN ONE TYPE OF PROSTHETIC VALVE IN THE SAME HEART
MS=MITRAL STENOSIS
MULT=MULTIPLE

MV=MITRAL VALVE
MVR=MITRAL VALVE REPLACEMENT
NIH=NATIONAL INSTITUTES OF HEALTH
No.=NUMERO:'NUMBER'
NS=NOT SIGNIFICANT
OP.=OPERATION
p=PROBABILITY
PROPOR.=PROPORTIONAL
p.(SING.)=PAGINA:'PAGE';pp.(PL.):'PAGES'
PVD=PULMONARY VALVULAR DISEASE
PVIE=PROSTHETIC VALVE INFECTIVE ENDOCARDITIS
PTS.=PATIENTS
PV=PULMONARY VALVE
RBB=RIGHT BUNDLE BRANCH
SCL=SCLEROSIS
SD=STANDARD DEVIATION
S-E=STARR-EDWARDS
sic=thus used, spelt
SJM=St JUDE MEDICAL
SMCs=SMOOTH MUSCLE CELLS
TV=TRICUSPID VALVE
TRICUSPID VALVULAR DISEASE
SPOND=SPONDYLITIS
SYNDR=SYNDROME
u=MICRO
VSD=VENTRICULAR SEPTAL DEFECT
UCT=UNIVERSITY OF CAPE TOWN
viz.=VIDELICET:'NAMELY';'THAT IS TO SAY';'IN OTHER WORDS'
%=PERCENTAGE

METHODOLOGY

METHODS APPLIED FOR THE STUDY OF THE PATHOLOGY OF HEART VALVE REPLACEMENT BY VALVULAR PROSTHESES.

1.HISTORICAL ASPECTS OF CARDIAC VALVE REPLACEMENT (See Chapter 1).

The broad outline of the history of surgical replacement of cardiac valves was examined by reviewing the literature in the following sequence : (a) early general historical landmarks, (b) indirect surgical techniques for mitral stenosis, (c) closed heart procedures for mitral regurgitation, (d) closed heart procedures for aortic stenosis and incompetence, and (e) open heart valve surgery on cardiopulmonary bypass.

2.STRUCTURAL DATA ON VARIOUS TYPES OF PROSTHETIC HEART VALVES (see Chapter 2).

Design criteria for the ideal prosthetic heart valve were summarized and the various types of commercially available mechanical and tissue heart valve prostheses were classified and their structure described. Details of the various models of the more widely used types of prostheses were also given. The advantages and disadvantages of prostheses which have not been used at Groote Schuur Hospital, Cape Town were high-lighted. An approach for the identification of prosthetic heart valves by pathologists based upon the morphological and radiological appearances of the prosthetic valve is also given.

3.INDICATIONS FOR HEART VALVE REPLACEMENT (see Chapter 3).

A.PATHOLOGY OF NATURAL CARDIAC VALVES WARRANTING REPLACEMENT BY VALVULAR PROSTHESIS.

The cardiac valvular pathology encountered in the 18,132 autopsies performed in the Department of Pathology, University

of Cape Town, during the 30 year period 1950-1979 was surveyed by reviewing the postmortem reports and where available the fixed specimens and/or photographs. The aetiology of the acquired valvular heart disease was noted, as well as the different functional classes and combinations of valvular lesions. The rates of rheumatic mitral stenosis per 100 autopsies for each of the 3 decades 1950-1959, 1960-1969 and 1970-1979 was determined. The various types of congenital heart disease encountered at autopsy over the same 30 year period was also recorded. The incidence of diseases, which are not necessarily treated by valve replacement or use of a valved conduit e.g., Fallot's tetralogy, were noted for comparative purposes.

B.CLINICAL INDICATIONS FOR HEART VALVE REPLACEMENT.

Clinical indications for heart valve replacement in the literature and those applied at Groote Schuur Hospital were discussed under the following headings : (i) Acquired valvular disease ; mitral valve disease, aortic valve disease, multivalvular disease, and tricuspid valve disease. (ii) Congenital heart disease.

C.MATCHING PROSTHESIS TO PATIENT.

The problem posed by the choice of an appropriate valve prosthesis in the unique circumstances posed by each individual patient was considered and guidelines were laid down for the use of tissue valves and mechanical heart valve prostheses respectively.

D.TRENDS IN CARDIAC SURGERY AT THE UNIVERSITY OF CAPE TOWN.

Trends in cardiac surgery at the University of Cape Town between 1951 and 1981 were analysed on the basis of the three reports(1-3) which have emanated from the Departments of

Cardiac Surgery and Medicine (Cardiac Clinic) of that institution. No data are available for the 5 year period 1966-1970.

E.TYPES OF PROSTHETIC HEART VALVES IMPLANTED AT THE UNIVERSITY OF CAPE TOWN BETWEEN 1962-1982.

The numbers of patients who received the different types of prosthetic heart valves in use at Groote Schuur Hospital were obtained by examination of the operation notes filed in the Department of Cardiac Surgery and the computerized data (available from 1976 onwards) of the Cardiac Clinic and the Department of Medical Informatics on patients who have undergone valve replacement at Groote Schuur Hospital.

F.AETIOLOGICAL DATA ON 100 CONSECUTIVE VALVE REPLACEMENT OPERATIONS.

One hundred consecutive patients who underwent heart valve replacement were randomly selected from the operation notes filed in the Department of Cardiac Surgery. The file randomly chosen was that for the year 1973 and the first 100 valve replacement operations in that file were analysed with regard to the aetiology of the native valvular disease which led to the valve surgery. The information on the pathology request form which accompanied the valve, and the pathologist's report after macroscopical and microscopical examination of the excised valve were also noted. These data were compared with one another and I then reviewed the pathological diagnosis of the likely aetiology of the native heart valve disease by combining the personally reviewed valvular histology, the macroscopical description and the operation note details regarding the appearance at operation of the diseased valve. The latter information had often not been supplied to the original pathologist who first examined the valve.

G.INCIDENCE OF ASCHOFF BODIES IN SURGICALLY SAMPLED CARDIAC TISSUE.

The incidence of granulomatous phase Aschoff bodies was examined in 2 groups of patients who had undergone heart valve replacement : (i) The first group consisted of one hundred consecutive patients who underwent heart valve replacement (same group who were studied regarding aetiology in section F above). I examined the histology of their atrial appendages, papillary muscles (where appropriate), and valves for granulomatous phase Aschoff bodies. (ii) The second group consisted of 468 patients who were operated upon during the years 1973-1982 and who had atrial appendages excised at the time of surgery for mitral stenosis or mixed mitral valve disease in which stenosis predominated. The incidence of Aschoff bodies as diagnosed by a variety of pathologists in this group of patients was recorded. I then reviewed the histology of those patients in whom Aschoff bodies had been diagnosed. In this review only granulomatous phase Aschoff bodies were accepted as positive Aschoff bodies. The criteria used for defining the granulomatous (proliferative) phase Aschoff body are essentially those of Fassbender(4) and Silver(5) and are summarized in Chapter 3, (Incidence of Aschoff bodies in surgically sampled cardiac tissue).

4.STUDY OF THE PRINCIPAL CAUSES OF DEATH AND THE MAJOR COMPLICATIONS CONTRIBUTING TO DEATH FOLLOWING HEART VALVE REPLACEMENT (see Chapters 4 to 15).

A total of 290 autopsied patients with implanted cardiac valvular prostheses was encountered between 1962 and 1982 (3.1% of 9291 autopsies). The types of valves inserted are listed in the Appendix (page 626). For the reasons given on page 450, 15 patients were excluded from the final analysis. Before describing the pathology of each type of cardiac valve implanted a table will be given indicating the cumulative survival rates and the cumulative embolism event-free rates of

all patients with that particular type of valvular prosthesis implanted between 1976 and 1982 at Groote Schuur Hospital. Actuarial methods described by Anderson et al.(6) were used to analyse the survival rates and thromboembolic complications.

The following approach to the pathology of heart valve replacement by prostheses was applied to the various types of prosthetic heart valves that have been implanted in patients at Groote Schuur Hospital,Cape Town. Detailed autopsy reports were available on each of the 290 patients with implanted cardiac valvular prostheses included in this study and the preserved hearts of 243 of these patients were available for re-examination. In each patient note was made of the age, race, sex and period of post-operative survival ; heart weight, presence or absence of thrombus on the prosthesis (and its anatomical situation), infective endocarditis, thromboemboli, organ infarcts, and other miscellaneous associated conditions. If a patient died within two weeks after valve replacement re-operation necessitated by failure of a previously inserted valve prosthesis, then that patient's death was attributed to the original valve prosthesis. Such a situation was encountered in 12 out of the patients studied. Methods used to evaluate the state of the coronary arteries and myocardium are described below. An attempt was made to pinpoint a single principal cause of death for each patient after valve replacement using the approach of Roberts(7). The causes of early deaths (less than one month after surgery) were compared with those occurring later. The principal causes of death were classified as follows using a modification of the systematic approach of Silver(5) :

(1) Error in pre-operative diagnosis e.g., unrecognized significant associated valvular disease.

(2) Error in operative technique. This may be related to the anaesthetic, to the extracorporeal circulation, or to the surgical technique and it may affect the valvular prosthesis, the valve rings, blood vessels or the conducting tissues.

(3) Valve prosthesis-related problems e.g., thrombus, infected vegetations, anticoagulant-related complications, or design/structural problems inherent in the prosthesis.

(4) Post-operative complications affecting non-cardiac organs.
(5) Complications unrelated to valve surgery.
(6) The final category consisted of those patients in whom no morphological cause of death was found.

I also applied this same classification of the principal causes of death to pathological reports in the literature which describe autopsy-determined causes of death in large groups of patients, who died following heart valve replacement. A few of the latter reports regarded early deaths as those occurring up to 2 months post-operatively.

The pattern of organ infarcts in my patients with implanted cardiac valvular prostheses was also analysed for each type of prosthesis and the incidence was compared with that observed in 103 non-operated subjects with valvular heart disease.

8. STUDY OF MISCELLANEOUS ALTERATIONS COMMON TO ALL PATIENTS WITH PROSTHETIC HEART VALVES.

A. CONDUCTION SYSTEM IN PROSTHETIC HEART VALVE REPLACEMENT, (see Chapter 17).

The atrioventricular node (AVN), the bundle of His and the proximal portions of the right and left bundle branches were examined microscopically in 41 patients ; 27 had implanted prosthetic heart valves and 14 routine autopsy patients served as controls. The 27 patients with valvular prostheses were divided into two groups. Group A consisted of 15 patients who died 5 days or less after valve replacement. Group B comprised 12 patients who died more than 5 days post-operatively. The control autopsy patients had died of diseases such as carcinoma of the lung, ruptured aortic aneurysm and pneumonia.

The tissue blocks for examining the AVN and bundle of His were fashioned according to the method of Hudson(8). A vertical incision was made through the upper inter-ventricular septum, which transected the bundle of His. Blocks were then taken backwards and forwards, to include the whole of the bundle and the AVN, as well as the bifurcation of the bundle into its left and right branches. According to Davies(9), in order to study the whole conduction system of the heart in an average case, between 200 to 300 sections will have to be examined from the 6000 to 9000 serial sections which are made available by this technique. Each such case will provide about 5 days' work for a competent histology technologist. Under the standard laboratory conditions which were available to me for the present study, it was impracticable to prepare serial sections of the conduction system of these 41 hearts. The technique was modified, so that the blocks of each heart were examined histologically by looking at representative sections cut at intervals of about 2 mm. Sections were stained by the haematoxylin-eosin and van Gieson (Verhoeff's counterstain for elastin) methods.

B.RENAL HAEMOSIDEROSIS (see Chapter 17).

Sections of the kidneys of 105 patients with implanted cardiac valvular prostheses were examined. These 105 patients comprised 50 patients with University of Cape Town (UCT) prostheses, 17 with mixed prostheses, 14 with Starr-Edwards valves, 7 with Lillehei-Kaster valves, 3 with Bjork-Shiley valves, 3 with Hancock prostheses, 5 with Carpentier-Edwards valves and 6 with St Jude Medical prostheses.

Two control groups of patients were studied. Firstly, the kidneys of 32 patients who died with advanced chronic rheumatic-type valvular deformities were examined for haemosiderin. None of these 32 patients had a prosthesis and most had died of cardiac failure. The second control group consisted of 21 consecutive routine adult autopsies.

All kidney sections studied were stained by the haematoxylin-eosin, periodic acid-Schiff methods and the amount of renal iron (haemosiderin) present was assessed on

sections stained by the Perl's Prussian blue method. Renal haemosiderosis was graded as follows : 0, no iron present ; +, scanty iron ; ++, moderate amounts of iron ; +++, abundant iron is present. For the purposes of this study the term °significant haemosiderosis' refers to moderate or abundant iron deposits. Sections of liver and spleen in these 159 patients were similarly evaluated for the presence of iron. Local lesions (e.g., infarcts) were disregarded in the assessment of iron content.

(iii) DISEASES OF THE MAJOR EPICARDIAL CORONARY ARTERIES (see Chapter 17).

A patient was regarded as having significant coronary arterial disease if there was 75% or more narrowing histologically of the lumen of one or more of the 3 major epicardial coronary arteries. The usual cause of such narrowing was atherosclerosis, but embolism and intimal (post-cannulation injury) fibrous intimal thickening were also looked for. The arteries were sectioned transversely at approximately 5 mm intervals throughout their length. Representative sections were taken of normal-appearing arteries and of all lesions of grade 2 severity or greater (25% or more luminal narrowing). The arterial sections were stained by the haematoxylin-eosin and van Gieson (Verhoeff's counterstain) methods ; the latter stain is referred to as the °elastic van Gieson' method in this study.

(iv) DISEASES OF THE SMALL CORONARY ARTERIES (see Chapter 17).

Abnormalities in the small (intra-myocardial) coronary arteries (haematoxylin-eosin sections) in the patients with prostheses were compared with the changes observed in the corresponding vessels in control patients with non-operated, similar natural valvular dysfunction to that which necessitated valve replacement in the study group and with

changes in 50 routine autopsy control patients.

(v) THE STATE OF THE MYOCARDIUM (see Chapter 17).

The state of the myocardium in 275 patients with prostheses was compared with that of 85 non-operated controls with native heart valve dysfunction similar to that which existed in the former prior to surgery. Myocardial necrosis in 45 randomly selected patients with implanted heart valves who underwent intermittent coronary arterial perfusion with blood from the pump-oxygenator machine (cooling to 32 degrees Centigrade) and had a beating heart during cardioplumonary bypass was compared with that in 42 patients treated by cold cardioplegic cardiac arrest. The latter hearts had been cooled down to less than 20 degrees Centigrade and cardiac arrest in diastole had been achieved by potassium administration. Necrosis and fibrosis were also assessed in 14 patients with intermittent and 21 patients with continuous coronary perfusion during bypass. Similarly, 16 patients with regularly beating hearts were compared with 21 others whose hearts fibrillated during bypass.

A minimum of five tissue blocks were taken from the same standard sites in the transversely sectioned ventricles of each heart at a level corresponding to the free margins of the mitral valve cusps. In 8 hearts of patients with University of Cape Town prostheses only between 2 and 4 random myocardial sections were available. The standard sites sectioned were the inter-ventricular septum, the anterior, lateral and posterior (inferior) walls of the left ventricle and the free wall of the right ventricle. Sites that were avoided were the vent wound at the left ventricular apex and the stumps of the papillary muscles if the atrioventricular valves had been replaced. The tissue was processed routinely for paraffin embedding. Two consecutive 5 micron thickness sections from each tissue block were stained by the haematoxylin-eosin (H.& E.) and elastic van Gieson (EVG) methods. (These two stains

were also used for the examination of coronary arteries,but H.& E. alone was used for the other routine autopsy sections). All slides used to assess the myocardium were labelled with a randomly selected non-sequential code number to conceal their identity, and examined by light microscopy.

MYOCARDIAL NECROSIS.

Three forms of acute myocardial damage were evaluated semi-quantitatively histologically : coagulative necrosis, contraction band necrosis (myofibrillar degeneration/coagulative myocytolysis) and colliquative myocytolysis(10). The severity of these 3 types of necrosis were graded on an arbitrary scale of 0 (no abnormality) to 3 (severe extensive, abnormality). Other forms of necrosis that were looked for included concentric, haemorrhagic, sub-endocardial necrosis(5) and the clinicopathological entity of the "stone heart"(5a).

MYOCARDIAL FIBROSIS.

Myocardial fibrosis of the left ventricle was appraised morphologically with the light microscope and an additional quantitative analysis was performed :

(A) The severity of four histopathological types of myocardial fibrosis(11) was estimated using an arbitrary scale of 0 (no fibrosis) to 3 (marked fibrosis). Four types of microscopical fibrosis were recorded : (i) Replacement fibrosis, which results from destruction of myocardium and its relationship to the surrounding myocardium suggests that it lies in a position previously occupied by muscle cells. Such fibrosis may be discrete or confluent. (ii) Interstitial fibrosis appears as fine strands of collagenous connective tissue encircling and separating individual muscle fibres. When mild in degree it tends to be focal and subendocardial. (iii) Perivascular fibrosis links up myocardial blood vessels

(adventitia to adventitia) and thereby delineates groups of muscle fibres into bundles or fascicles. (iv) Plexiform fibrosis is noted in areas of myofibre disarray similar to that seen in hypertrophic cardiomyopathy. Foci of collagenous fibrous tissue of irregular size and shape with jagged borders lie interlaced between myocardial fibres.

(B) The amount of fibrous connective tissue in the myocardium of the left ventricle in patients with prostheses and in non-operated controls was also determined on a morphometric basis. Any tissue is made up of a compact mass of three dimensional objects which can be penetrated by fixative, and cut in thin sections,still preserving the two dimensional relationships between structures. The section, however, cuts through the tissue in a random fashion and thus presents flat profiles of the components. Simple quantitative relations exist between the average dimensions of large numbers of profiles of particular organelles. Thus, the aggregate of profiles per unit area of tissue is quantitatively representative of the aggregate of organelles contained in the unit volume of tissue, so that the measurements on sections of tissue can be interpreted in terms of structural dimensions by means of mathematical relationships(12,13).

In simple terms, a volumetric analysis of tissue sections is achieved by point counting. This analysis is done by superimposing a point lattice (a test grid,which is a grid of lines drawn at right angles to each other using the intersections as the point lattice) over a microscope image or photographic print of the section,and counting the number of points (intersections) which happen to fall on the component being investigated. The ratio of points falling on the component °i' being investigated to the total number of points falling on the test tissue within the area of the test grid, i.e. Pi/Ptotal is equal to the volume of component °i' in the tissue volume encompassed by the test grid (14,15).

Ten random fields from two different sections, one from the anterior wall and the other from the posterior (inferior)

wall of the left ventricle were studied at a magnification of 400X. The connective tissue content was determined by using a square grid (an ocular micrometer) of 121 points inserted in the microscope eyepiece. By this method, a total of 1210 points was counted in each specimen. The percentage connective tissue was calculated using the relationship:

$$Vct = \frac{Pct}{Ptot} \times \frac{100}{1}$$

where Vct is the volume of connective tissue per unit volume of cardiac muscle, Pct the number of points falling on connective tissue and Ptot, the number of points in the point lattice. These fields were taken from areas of myocardial tissue in which no large blood vessels were encountered and which were well clear of the endocardium. This was done to avoid the large aggregations of connective tissue which are normally found at these sites.

ASCHOFF BODIES.

The presence or absence of granulomatous (proliferative) phase Aschoff bodies (as defined above in section 3 G) was noted in the myocardial sections of the hearts containing valvular prostheses.

(vi) ORGAN INFARCTS.

The distribution pattern of organ infarcts in patients with prostheses and in 103 non-operated controls with similar native valvular dysfunction was also studied.

(vii) PANCREATIC FIBROSIS RELATED TO CHRONIC HEART FAILURE.

The amount of fibrous tissue in the pancreas was assessed morphometrically using the (ocular micrometer) point-counting method and counting 1210 points in each case (using the same method that was used to assess myocardial fibrosis above). Two groups of autopsy patients were assessed : firstly 112 patients with implanted prosthetic heart valves, (178 patients were excluded from this analysis due to autolysis or the lack of a section of the pancreas) and secondly in 20 routine autopsy control patients. The amount of pancreatic fibrosis was scored as follows : 0 = normal ; 1 = mild fibrosis ; 2 = moderate ; and 3 = severe fibrosis. Patients with other possible causes of pancreatic disease were excluded as controls e.g., alcoholism, cortisol therapy or gallstones.

6. METHODS USED TO STUDY UCT FORMALDEHYDE-TREATED XENOGRAFT PORCINE AORTIC VALVE BIOPROSTHESIS IN THE MITRAL POSITION, (see Chapter 9)

Aortic valves were obtained from pigs aged 1 to 2 years and weighing between 150 and 300 kg. After trimming, the valves were mounted according to the method of Ionescu et al.(16), packed with cotton wool and immersed in 4% formol-saline (buffered at pH 5.6). Following implantation of a number of these locally prepared xenograft prostheses in patients, subsequent dysfunction led to a number of the valves being surgically removed and 11 were submitted for pathological evaluation.

The 11 valves were submitted in 5% formaldehyde solution for pathological examination. Each valve, still mounted on its Dacron cloth-covered titanium ring, was examined with the naked eye for signs of thrombosis, rupture or incompetence. Any other abnormal feature was also noted. Sections taken from the centre of each of the 3 valve cusps were stained by the haematoxylin-eosin, alcian blue and elastic van Gieson

methods. A series of 14 control pig aortic valves were similarly examined ; nine of these valves had been frame-mounted and treated with formaldehyde in an identical manner to those used in the 11 patients.

Transmission electron microscopy was performed on cuspidal tissue from two of the failed xenograft valves (cases 2 and 10) and on three of the control valves. This was considered worthwhile in studying changes in the collagen, rather than cellular detail, of the formaldehyde-fixed material. Blocks for electron microscopy, about 2mm thick, were cut from the valve cusps in such a fashion as to include the full thickness of the cusp. The blocks were post-fixed in osmic acid (Palade's fixative) for one hour, dehydrated in graded ethanols and embedded in Araldite. The blocks of embedded tissue were orientated for sectioning so that the fibrosa of each cusp was included in the section. Ultrathin sections were stained with Reynold's lead citrate and with uranyl acetate.

7. METHODS USED FOR THE EVALUATION OF HANCOCK AND CARPENTIER-EDWARDS BIOPROSTHESES, (see Chapters 10 and 11).

The xenograft valves were examined and photographed in situ in the autopsied hearts, then excised and x-rayed for detection of calcification which might have not been recognized naked eye. Sections for light microscopy were taken from the mid-portion of each cusp from the free edge to the junction with the host tissue. Such sections were fixed in 5% buffered formaldehyde and processed in the routine manner. Sections were stained by the haematoxylin-eosin, elastic van Gieson, von Kossa, Martius scarlet blue and sulphated alcian blue methods.

Tissue samples of the cusps taken for electron microscopy were treated in an identical manner to that described above for the formaldehyde-treated porcine xenograft aortic valve.

8. METHODS USED FOR THE EXPERIMENTAL EVALUATION OF THE MITROFLOW BOVINE PERICARDIAL XENOGRAFT HEART VALVE PROSTHESIS, (see Chapter 16).

GROUPS OF BOVINE PERICARDIAL XENOGRAFT VALVES EVALUATED :

(i) ORIGINAL "PILOT PROCESS" : these 7 Mitroflow valves were prepared by a proprietary process of fixation, the details of which have not been divulged by Mitral Medical Inc. All were implanted in the mitral position.

(ii) "PROCESS G" : This process was based on a simple glutaraldehyde-fixation. No attempt was made to enhance the pericardial tissue for anticalcific or antithrombogenic characteristics.

A. The pericardium was shipped to the manufacturing plant from the slaughterhouse either (a) dry on ice, or (b) in a 25% isopropanol solution in phosphate buffered saline containing ethylene diamine tetra-acetic acid (EDTA). Option (b) attempts to minimize microbial growth and enzymatic degradation by micro-organisms or autolysis. Isopropanol dehydrates and stabilizes the tissue, but also dissolves lipids and may change the surface properties of the tissues.

B. On arrival at the plant the tissue was washed in phosphate buffered saline (PBS) to remove blood and loose debris, and stored for time periods ranging from 40 - 96 hours. Some valves were washed with 25% isopropanol in PBS. (Isopropanol will continue to dissolve lipids, stabilize the tissue and have mild bacteriostatic properties, but autolysis is not inhibited).

C. The tissue was cleaned down and stored in PBS, 25% isopropanol in PBS or in PBS containing EDTA. The latter provides calcium chelating properties which will suppress both bacterial and autolytic enzyme degradation.

D. The valves were then assembled in the same types of solutions and fixation was carried out in 0.2% glutaraldehyde in PBS for 11 days or in 0.4% glutaraldehyde in 25% isopropanol in PBS for up to 21 days.

E. Sterilization was carried out in 2% glutaraldehyde, 3% formaldehyde and 20% isopropanol in PBS at pH 5.7 for 48 hours.

F. The valves were packaged in 4% formaldehyde at pH 5.7

(iii) "PROCESS F" : This process of tissue fixation by glutaraldehyde relies on cross-linking of collagen molecules via the epsilon-amino groups of lysine after biological species designed to inhibit the calcification tendency have been attached through pendant carboxyl groups of aspartic and glutamic acid residues.

A. The tissue was transported from the slaughterhouse to the plant and rinsed in 25% isopropanol in PBS within 6 hours of harvesting. Gross cleaning was performed in 25% isopropanol in PBS and the final clean down and storage was carried out in PBS containing EDTA.

B. Valve assembly was carried out in PBS containing EDTA.

C. The development of anti-calcification properties was attempted as follows : firstly the tissue was infiltrated with 1:6 diaminohexane in PBS in order to increase the concentration of primary amino groups within the tissue matrix. Secondly, the tissue containing the proposed increased concentration of primary amino groups was equilibrated with 1% chondroitin-6-sulphate in PBS at 4 degrees Centigrade and pH 7.4 overnight. 1-ethyl-3-(3-dimethylamino propyl) carbodiimide was used to couple the chondroitin sulphate through its carboxyl groups to the primary amino groups of the modified collagen. This should produce a more hydrophilic surface containing sulphate groups, which in themselves may reduce protein adsorption and therefore lower the thrombogenic and calcification tendencies of the xenograft.

D. The valve was stored in PBS containing EDTA and

sterilization consisted of 48 hours treatment in 2% glutaraldehyde, 3% formaldehyde and 20% isopropanol in PBS at pH 7.4.

E. The valve prosthesis was packaged and shipped in 4% formaldehyde in sodium acetate/acetic acid buffer at pH 5.6.

(iv) "PRE-HUMAN PROCESS" : No details are available regarding this latest method of preparation of the Mitroflow valve prosthesis. All of the Mitroflow valves in this series, apart from one valve in this group, were implanted in the mitral position - the one exception being a tricuspid implant.

(v) CONTROL XENOGRAFT VALVULAR PROSTHESES : Four commercially available Ionescu-Shiley pericardial heart valves were implanted in baboons as controls. Three were placed in the mitral position and one in the tricuspid position.

OPERATIVE TECHNIQUE

Thirty-five Mitroflow (Mitroflow Medical Inc.) bovine pericardial heart valve prostheses were implanted in Chacma baboons between October 1980 and July 1982 by Dr J. Hassoulas of the Department of Cardiac Surgery, Groote Schuur Hospital and University of Cape Town. All, apart from one tricuspid implant, were inserted in the mitral position. The Mitroflow valves used all had a diameter of 21 mm. A further four (size 19 mm) Ionescu-Shiley pericardial xenograft cardiac valve prostheses (Shiley Laboratories Inc.) were implanted as controls, 3 in the mitral position and 1 in the tricuspid position.

The Chacma baboons which received the implanted valves had a mean body weight of 21.9 Kg (S.D.= 5.7) with a range of 15 to 32 Kg. Standard cardiopulmonary bypass techniques were used with cardioplegic myocardial protection and the body temperature was reduced to 28 degrees Centigrade. The mitral valve was approached through the usual left atrial incision on the right heart border. In order to augment the strength of

the normal mitral valve for suturing, substantial leaflet tissue was left behind. Sutures were arranged in an interrupted fashion and as a figure-of-eight. The test and control valves were all inserted in a similar fashion. Once bypass had been discontinued, and there was haemodynamic stability, a left atrial and left ventricular apex infusion catheter were inserted for pressure measurements. These catheters were connected to Statham P23H pressure transducers, the left atrial and left ventricular pressures were recorded, and the transvalvular gradient was calculated.

Post-operatively the animals were carefully monitored and were eventually sacrificed selectively at pre-determined time intervals. Left and right heart catheterizations were performed immediately prior to sacrifice in all animals and some animals were also catheterized earlier during the post-operative survival period. For the pre-sacrificial catheterization a 7F thromodilution cardiac output catheter (American Edwards Laboratories) was inserted and cardiac output was estimated using a model 9510 American Edwards cardiac output computer. Left ventricular pressure measurements were obtained via a small infusion catheter inserted into the left ventricle through a small stab wound and connected to a P23H Statham pressure transducer. These measurements, together with the wedge pressure, were used to calculate the pre-sacrifice trans-valvular gradient. The percentage reduction in the valve orifice area was also calculated. The animals were heparinised prior to sacrifice. The heart and lungs were removed en-bloc for histopathological examination and the abdominal organs were examined grossly for signs of passive congestion or infarction.

PATHOLOGY

MACROSCOPICAL EXAMINATION

On receipt in the Department of Pathology, the fresh

heart and lungs of each animal were examined macroscopically. The heart and lungs were separated and the heart was opened in the routine manner following the course of the blood flow within the heart. The interior of the heart was washed gently in fresh water and the implanted heart valve was photographed in situ. The first 4 Mitroflow valves examined were also x-rayed to make sure that one was not missing minute amounts of calcification not detected naked eye or histologically. All of these x-rayed valves were negative for calcification. Each prosthetic valve was excised including a rim of surrounding host tissue.

LIGHT MICROSCOPICAL EXAMINATION

A section was taken from the mid-portion of each valve cusp showing any naked eye abnormality. The section extended from the free margin to the base and included the junction with the host tissue. Since I had been requested to leave the prosthesis as intact as possible for re-examination by Mitral Medical Inc., in instances where the cusps looked normal, only one cusp was sampled. The valve samples, together with sections of lung and of other organs, were fixed in 5% buffered formaldehyde and processed in the routine manner for paraffin-embedded histological sections. The latter were stained by the haematoxylin-eosin, elastic van Gieson and Martius scarlet blue methods.

TRANSMISSION ELECTRON MICROSCOPY

Tissue samples of the cusps taken for electron microscopy were treated in an identical manner to that described above for the formaldehyde-treated porcine xenograft aortic valve. Two Mitroflow valves of the pilot series, 1 of the "F" process, 2 of the pre-human and 1 Ionescu-Shiley control valve were examined ultrastructurally. The duration of implantation of these valves are indicated in Table 16.4 of Chapter 16.

SCANNING ELECTRON MICROSCOPY

Scanning electron microscopy was performed upon 3 Mitroflow valves derived from the "pilot", "F" process and "pre-human" series - the valves having been implanted for periods of 6, 36 and 122 days respectively. Samples of the valve cusps of these 3 valves, which were taken from areas devoid of thrombi, were freeze dried and then coated with evaporated carbon and evaporated gold. The surface examined was the contact surface of the cusps, which is the portion of the bovine pericardium, which has been trimmed of attached fibroadipose tissue during manufacture.

9. CONTROL PATIENTS (See too Appendix, page 627).

Control patients were studied in an identical manner to the patients with implanted cardiac valvular prostheses.

A. ORGAN INFARCTS

One hundred and three autopsy patients with significant valvular heart disease, excluding patients with infective endocarditis, served as controls for studying the distribution of organ infarcts due to thromboembolism. Eighty-seven percent had a rheumatic aetiology for the valvular disease. Mitral valvular disease was the dominant lesion in 60 patients and aortic valvular disease was present in 43.

B. CONDUCTING TISSUES

Fourteen routine autopsy control patients, who had died of a variety of diseases e.g., carcinoma, pneumonia and ruptured aneurysm, served as controls for examination of the conducting tissues.

C. RENAL HAEMOSIDEROSIS

Two groups of control patients were studied. Firstly, there were 32 patients with advanced chronic rheumatic-type valvular deformities, most of whom had died in congestive heart failure. Secondly, 21 consecutive routine autopsies were studied.

D. SMALL CORONARY ARTERY DISEASE

Three control groups of patients were evaluated. Thirteen patients with floridly active granulomatous phase Aschoff bodies comprised the first group ; 26 patients with healed rheumatic fever (no Aschoff bodies) formed the second group. The latter patients all had well documented histories of repeated attacks of acute rheumatic fever and also had severe mitral stenosis at autopsy. Twenty routine autopsy patients formed the third group.

E. MYOCARDIAL NECROSIS AND FIBROSIS

Eighty-five autopsy patients with uncorrected valvular heart disease which had led directly to the death of the patient served as controls for evaluation of the ventricular myocardium in patients with valvular prostheses. Thirty-one patients had mitral valvular disease and the other 54 had aortic valvular disease.

F. PANCREATIC FIBROSIS

Twenty consecutive routine autopsy patients served as controls, excuding patients with chronic excessive ethanol ingestion, gallstones or idiopathic chronic pancreatitis.

10. CONTROL ANIMAL TISSUE

A. FORMALDEHYDE-TREATED PORCINE AORTIC XENOGRAFT VALVES

Fourteen aortic valves from adult Landrace pigs were used as controls. Five aortic valves were obtained freshly from the abbatoir and fixed promptly in 5% buffered formaldehyde solution. Nine valves had been frame-mounted and treated with formaldehyde in an identical manner to the 11 test valves that had been implanted in human patients.

B. IONESCU-SHILEY BIOPROSTHESES

Four commercially available Ionescu-Shiley bovine pericardial heart valves were implanted into baboons as controls for assessment of the Mitroflow bovine pericardial heart valve.

11. STATISTICAL METHODS.

The Chi-square evaluation was performed upon data obtained by morphological assessment (using a semi-quantitative scoring system) of various forms of myocardial necrosis and fibrosis. The t statistic for two means (null hypothesis) was used to test for a significant difference between values obtained by morphometry (point-counting) of the fibrous tissue component of the myocardium and for differences in heart weights. Actuarial methods described by Anderson et al.(6) were used to analyse the survival rates and thromboembolic complications of patients with implanted valvular prostheses.

CHAPTER 1.

HISTORICAL ASPECTS OF CARDIAC VALVE REPLACEMENT

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INTRODUCTION

An old platitude about the growth of surgery(1) suggests that in each decade since 1870 surgical advances have occurred in the form of a steady march as some new area of the body was opened to surgical correction. However, cardiac surgery differs ; it has undergone a convulsive and revolutionary advance about once every 5 years. Each advance is associated with the names of one or two individuals : constrictive pericarditis (Churchill in 1933), the patent ductus arteriosus (Gross in 1938)(2), closed mitral repair (Harken in 1948), the pump oxygenator (Gibbon in 1953)(3), valve prostheses (Hufnagel 1952 ; Harken and Starr,1958), reconstruction of the congenitally malformed heart (Kirklin,1963), cardiac transplantation (Barnard,1967), and saphenous vein bypass grafting of coronary arteries (Favoloro,1970). In this review I shall focus on the principal historical landmarks in the history of surgical replacement of diseased heart valves.

The chief landmarks in the history of heart valve replacement will be dealt with under the following headings : (i) general historical landmarks ; (ii) indirect surgical techniques for mitral stenosis culminating in closed direct surgery for mitral stenosis in 1949 ; (iii) closed heart procedures for mitral regurgitation ; and (iv) closed heart procedures for aortic stenosis and incompetence. (v) The introduction of cardiopulmonary bypass by Gibbon in 1953 ushered in the era of open heart valve repair for mitral and aortic valvular disease(3). Partial replacement of the mitral valve with immobile and mobile prostheses, mono- and multicuspid valves as well as valves with artificial chordae tendineae were superceded by the successful insertion of a

ball-valve prosthesis by Starr in the mitral position about two decades ago. Earlier in the same year (1960), Harken had been the first to successfully replace a diseased aortic valve with a caged-ball prosthesis.

1.GENERAL HISTORICAL ASPECTS(4-9):

The pathology of mitral stenosis was first described by Raymond Vieussens at Montpelier in 1715 in a textbook entitled "Traite nouveau de la structure et des causes du mouvement naturel du coeur". In 1882, Block sutured cardiac wounds in experimental animals. However, cardiac surgery had an uphill battle against the dogma of the day. In 1893 Billroth(10) stated that "Any surgeon who would attempt an operation on the heart should lose the respect of his colleagues." Paget (1896) wrote that "the surgery of the heart has probably reached the limits set by nature to all surgery."

Undeterred by this, Rehn repaired a right ventricular stab wound in 1896. In 1898, Samways proposed the surgical relief of mitral stenosis. In 1902, Brunton opened stenosed mitral valves in cadavers and operated on the normal mitral valve of dead cats using a transventricular tenotomy knife. In the same year Sauerbruch and Meyer used pressure chambers to overcome the problem of surgically induced pneumothorax. In 1908, Cushing and Branch unsuccessfully operated on a dog with mitral stenosis. This is the first recorded operation for acquired mitral valve disease. In 1909 Meltzer and Auer introduced an endotracheal tube which simplified gas anaesthesia for thoracic surgery. In 1910, Carrel suggested that a finger may be used to dilate a stenosed mitral valve. Prior to this the use of instruments had always been stressed. Carrel, who was awarded the 1912 Nobel Prize for Physiology and Medicine for his accomplishments in the new field of cardiovascular surgery, had perfected the basic techniques of vascular anastomoses and patch graft angioplasty on the canine thoracic aorta. Using 2-3 minutes of ischaemic cardiac arrest,

he had subsequently either cauterized the aortic valve, sutured pulmonary valve leaflets, patched the right ventricular outflow tract, or positioned a graft between the cardiac apex and the descending thoracic aorta.

In 1913 Doyen attempted the first operation on a human cardiac valve. The patient died early post-operatively and autopsy revealed muscular subpulmonary stenosis rather than valvular stenosis. Tuffier performed the first successful operation on a human heart valve in 1914 using a finger to invaginate the ascending aorta and to dilate a stenotic aortic valve.

Important advances also occurred in the ancillary services : In 1929, Forssmann(11) performed the first documented human cardiac catheterization (on his own heart). Thereafter, Cournand(12) and Richards(13) propagated the use of this new technique in the study of patients with congestive heart failure. These three men were awarded the Nobel Prize for Medicine in 1956 for this work. However,Bleichroeder(14) had performed the same experiment as Forssmann as early as 1912 at a time when no radiological assistance was available. Although this work was acknowledged by Forssmann in an addendum to his publication, the courageous achievement of Bleichroeder has been largely ignored. In 1933, Charles and Scott(15) purified heparin so that it could be used clinically for anticoagulation e.g., for extracorporeal circulation. The first blood bank was established by Fantus(16) in the United States of America in 1937.

MITRAL STENOSIS.

CLOSED HEART PROCEDURES FOR MITRAL STENOSIS

In 1922, Allen and Graham(17) employed a cardioscope to inspect the mitral valve. In 1923, Cutler(18) performed the first successful operation for mitral stenosis using tenotome knives and a cardiovalvulotome inserted through the left

ventricular apex. Mitral regurgitation was a serious complication of this procedure. In 1925 Souttar performed the second successful operation for mitral stenosis using a transatrial approach(19). He was able to detect severe mitral incompetence and dilated the orifice with his right index finger, rather than magnifying the incompetence by cutting into the valve. His patient was the first to have a successful result from such an operation. During the period 1930 to 1945, cardiac valve surgery was in the doldrums due to the initially poor results. Thirty years later one of Cutler's co-workers Dr C.S.Beck(20) said of the cardiovalvulotome which he had helped to develop : "The creation of this instrument probably delayed the development of the operation for mitral stenosis by some twenty years." Powers(21-23) documented the serious consequences of producing mitral insufficiency when operating for mitral stenosis. His work on dogs was performed at the Peter Bent Brigham Hospital where Cutler had earlier done his pioneering efforts. Unfortunately no successful operation was developed.

INDIRECT SURGICAL TECHNIQUES FOR MITRAL STENOSIS

Attempts to relieve the symptoms of mitral stenosis other than by valve directed surgery had been suggested as early as 1913 by Jeger, who proposed inserting a valved vein between a pulmonary vein and the left ventricle to decompress the left atrium. Litwak created such a graft in a dog, but the graft thrombosed. No such attempt was made in humans. In 1913, Schepelmann linked the two atrial appendages of a rabbit with an aortic graft. In 1926 Dmitrieff perforated the atrial septum both via the jugular veins and at thoracotomy. Such a procedure was performed by Harken et al. in 1948(24) and by Bailey(25) in the following year, but later the efficacy of the operation was questioned(26). Similar results were achieved by Sweet(27) and d'Allaines(28) in man by anastomosing a branch of a pulmonary vein to the azygous vein.

Tricuspid valvulotomy was proposed by Cossio and Perianes(29) as a palliation for mitral stenosis.

THE MODERN ERA : 1949 ONWARDS

The current era of valve surgery began in 1949 when Bailey(25), Harken(24) and Brock(4,30), all working independently, first successfully repaired stenotic mitral valves. Bailey(25) performed a successful mitral commissurotomy using digital palpation to guide the ensheathed mitral valve cutting blade. Murray excised portion of the posterior mitral leaflet and reduced incompetence by placing an everted vein graft containing palmaris longus tendon across the left ventricular cavity so that it occluded the mitral valve orifice during ventricular systole. Harken(24) performed a similar operation 6 days after Bailey using a valvulotome to cut the fused commissures. Only a few months after the successful operations of Bailey and Harken, Brock(30) performed finger fracture of a stenotic mitral valve using experience gained with successful operations for pulmonary stenosis. (Sellors(31) and Brock(32) had divided the stenosed pulmonary valve with an instrument introduced through a small incision in the right ventricle).

Between 1950 and 1955 several hundred successful mitral commissurotomies were performed world-wide. Further refinements in technique,improved patient selection and preparation, plus improved post-operative care followed thereafter. In 1954, Dubost et al.(33) described a transatrial mechanical dilator for correcting mitral stenosis. By 1962 he had achieved several hundred valvulotomies with only a 2% mortality rate(34). In 1959, Logan and Turner(35) described their results with the mechanical dilator using a transventricular approach. Initially they had used a dilator devised locally by Dr M.Brown, but later Dubost's instrument

became available. The dilator first used had a maximum spread of 3.5 cm and this was often too small to fully open both commissures. An ideal spread of 5 cm was provided by the instrument later designed for them by Mr O.S.Tubbs(35,36). In time the Tubbs' dilator became widely used world-wide.

MITRAL INCOMPETENCE

Although many of the experimental studies on the mitral valve involved the production of mitral insufficiency, the concept of the surgical relief of this lesion was slow in developing(9). For many years surgeons erroneously believed that mitral incompetence was not a significant lesion and that it had little effect on the heart. In 1910, Carrel(37) tried to relieve mitral incompetence in dogs by producing a slight stenosis of the upper part of the left ventricle by resecting part of the mural muscle.

CLOSED HEART PROCEDURES FOR MITRAL REGURGITATION

These took the form of blindly inserting autogenous or plastic materials to support or augment the posterior mitral leaflet, or of using a circumferential suture to narrow the mitral valve ring. In 1949 Templeton and Gibbon(38) reported cardiac valve reconstruction by venous and pericardial grafts. Atrium was also used later by others for such "trans-ventricular tamponage". Bailey et al's(39) "commissurorrhaphy" operation involved suturing the valve leaflets together using strips of pericardium. During the 1950s a variety of plastic materials of various sizes and shapes were used to support or augment the posterior mitral leaflet e.g., methyl methacrylate (Lucite(40,41), Plexiglas(42)) and polyvinyl formalinized plastic (Ivalon(43,44)). This technique was used clinically for mitral incompetence in the early years of open heart surgery. In 1955, Jordan and Wible(45) sited a nylon leaflet mounted on an

Elgiloy spring frame below the mitral valve to prevent mitral regurgitation.

Between 1955 and 1957, Kay and Cross(46) and Nichols(47) obtained palliative results using a closed-heart version of what later was called posteromedial annuloplasty(4). In 1958 Davila et al.(48) described a technique of external circumferential suture (using umbilical tape) of the mitral valve ring to correct incompetence. Unfortunately the operation was followed by a high rate of recurrence of the regurgitation. All of the closed techniques for the correction of mitral incompetence were unsatisfactory and no further surgical advances were made until bloodless field mitral valve surgery became possible.

CLOSED HEART PROCEDURES FOR AORTIC STENOSIS AND REGURGITATION

In 1948, Smithy et al.(49) devised a method of performing transaortic and transventricular aortic valvotomy in experimental animals. In 1950, Bailey et al.(50) reported their results with retrograde aortic valve incision and dilatation. This approach was abandoned due to arterial dissections and the development of aortic incompetence. A transventricular approach yielded better results(51).

Enormous strides towards the advent of valvular surgery were made in the 1950s. Bailey and Likoff(52) and Taylor et al.(53) unsuccessfully tried to alleviate aortic incompetence by tying a suture around the base of the aorta to narrow the aortic ring. Campbell(54) and Hufnagel(55) independently designed artificial heart valves composed of a mobile, spherical poppet within a Lucite tube using the caged-ball principle devised by Williams(56) in his bottle stopper patent of 1858. Campbell and Hufnagel initially tested their prostheses in the descending thoracic aorta of dogs. On September 11, 1952 Hufnagel (57) ushered in the era of prosthetic valve surgery by successfully inserting his caged-ball valve into the descending thoracic aorta of a

patient suffering from severe aortic incompetence.

In 1953 Gibbon(58) dramatically anounced the first successful use of total cardiopulmonary bypass for bloodless field intracardiac surgery in humans. This, together with Hufnagel's surgical success with the caged-ball aortic prosthesis(57) set the stage for future surgical attempts to replace diseased heart valves with artificial substitutes. In the succeeding ten years more advances took place in this type of surgery than had occurred throughout the preceding centuries.

The provision of a pump to take on the function of the heart was relatively simple compared to the problems faced in developing an artificial lung. The artificial lung developed by Gibbons was subsequently incorporated into the Gibbons-Mayo pump. Lillehei and colleagues(59) in Minnesota initially made use of a human donor to supply oxygenated blood in 30 patients with complicated congenital heart lesions and later developed their bubble oxygenator. Melrose(60) published details of his heart-lung apparatus. Later, following a fruitful collaboration with Gerbode(61), his machine gained worldwide acceptance. Modifications and refinements of the heart-lung machine continued to be made during the 1960s and 1970s and the next major step was the development of the membrane oxygenator.

OPEN HEART VALVE REPAIR PROCEDURES

As a result of the above two major milestones, surgeons were stimulated to try and correct valvular lesions by directing their attentions to the abnormal valves themselves, particularly the aortic valve(62-64).

OPEN HEART SURGERY FOR MITRAL VALVE DISEASE

Between 1956 and 1968 the heart-lung bypass machine was used initially for operative correction of congenital valvular

diseases(4), but later it was also used for acquired valvular diseases(65-72). Lillehei and the Minnesota group at first performed paediatric intracardiac surgery using another person as an oxygenator (controlled cross-circulation). The De Wall-Lillehei bubble oxygenator, which was introduced later, was simple to use ; it was also cheap and disposable, but perfusion rates were slow. The perfusion equipment which has now superceded it is simpler and more reliable and these membrane oxygenators have faster perfusion rates. The first successful open heart operation for acquired mitral valve disease was performed on 29th August,1956 at the University of Minnesota by Dr C.Walton Lillehei(66).

MITRAL STENOSIS

Open heart surgery for mitral stenosis was used to break down fused commissures or to remove calcium from the edges of the valve. Because the site of commissural fusion was often difficult to localize, some surgeons still used a dilator. However, direct vision was of great assistance in surgical correction of areas of subvalvular fusion(9). In recent years there has been a swing towards doing open mitral valvotomies in all patients with significant mitral stenosis(73,74).

MITRAL INCOMPETENCE

Numerous open reconstructive techniques have been attempted in order to correct the regurgitant mitral valve. These include : (a) repair by direct suture of cuspidal tears or perforations due to infective endocarditis(75,76), trauma(77) e.g., after mitral commissurotomy for rheumatic fever(9). (b) Increasing the surface area of the deficient leaflet : Nichols et al.(68) inserted an elliptical segment of compressed polyvinyl sponge between the annulus and the leaflet. Sauvage and Wood(78) sutured patches within shrunken leaflets to augment the surface area. Associated chordal

abnormalities frequently limited the operative results. (c) Repair of ruptured chordae tendineae, (which are encountered in about 20% of patients with pure mitral incompetence(79)), was attempted by immobilizing the flail area(80), resuturing chordae to the papillary muscle(68), plicating the ruptured leaflet(81) with posteromedial annuloplasty(82), or constructing artificial chordae of silk(83), Dacron(84) or Teflon(85). (d) Narrowing the mitral annulus increases the area of cuspidal apposition and this operation had been earlier performed as a closed procedure.

Lillehei et al.(66) were the first to perform mitral annuloplasty under direct vision. Heavy through-and-through silk sutures were placed in the mitral ring at one or both commissures. According to Lefrak and Starr(4) annuloplasty procedures helped 50% of patients with moderate or severe isolated mitral regurgitation, especially those with ring dilatation, but it was less successful if the cusps were severely fibrosed or shrunken. Poor results(83,86,87) were obtained using artificial chordae prepared from silk, Teflon or Dacron fibre, but McGoon's plication procedure gave better results(81). Later failures led to technical modifications such as using Ivalon or Teflon to buttress the sutures and prevent them cutting through the tissues(70,88). However, the annuloplasty technique(9) that has provided the best long-term results is postero-medial annuloplasty or modifications thereof(71). The procedure achieves mitral annular narrowing at the expense of the posterior leaflet and there is little danger of disruption of the sutures which are placed in the tough, fibrous mitral ring.

REPLACEMENT OF THE MITRAL VALVE WITH A PROSTHESIS

Unfortunately, the above described reconstructive techniques were not applicable to most rheumatic patients with calcified, immobile, stenotic and incompetent mitral valves.

(A) PARTIAL REPLACEMENT OF THE MITRAL VALVE WITH AN IMMOBILE PROSTHESIS

This technique was only applicable to those patients whose mitral incompetence was due to a shrunken, immobile posterior leaflet, with the anterior leaflet remaining pliable and mobile. Gott et al.(89) sutured a cylinder of compressed Ivalon underneath the leading edge of the posterior leaflet. Barnard and Schrire(90,91) described how an immobile Ivalon baffle (Figures 1.1 and 1.2) could be sutured so as to augment a shrunken posterior mitral valve leaflet. During left ventricular systole the anterior leaflet closes against the baffle. Barnard(91) sutured a cylindrical piece of compressed Ivalon on the ventricular surface of the posterolateral part of the mitral ring in four patients. In another 12 patients a spindle-shaped piece of compressed Ivalon was attached to the non-ventricular surface of the valve. Infection was a significant complication in some of these patients(91). This operation(66) and related variants thereof(85,92,93) gave poor late results due to infection, mitral stenosis and emboli. Mitral valve replacement superceded this operation.

Figure 1.1 : Ivalon sponge prosthesis compensates for deficient posterior mitral valve leaflet.

Figure 1.2 : Bisected Ivalon sponge prosthesis and posterior mitral leaflet are viewed in profile.

(B) PARTIAL REPLACEMENT OF THE MITRAL VALVE WITH A MOBILE PROSTHESIS

Partial replacement of the mitral valve with a mobile prosthesis was attempted in order to try and avoid the mitral stenosis which complicated partial replacement of the valve with an immobile prosthesis. Silicone rubber (Silastic) leaflets, Silastic-covered Teflon leaflets with attached chordae tendineae and knitted Teflon leaflets with chordal extensions were unsuccessfully tested in animals and were not used in humans(9). Techniques used clinically included replacement of the posterior mitral leaflet with knitted Dacron(94) or the use of autologous pericardial leaflets for the same purpose(95,96).

(C) TOTAL REPLACEMENT OF THE MITRAL VALVE WITH A PROSTHESIS

EXPERIMENTAL RESULTS :

Experimental mitral valve replacement in the dog yielded disappointing results(9) due to problems with perfusion, operative techniques, poor valve design and inappropriate selection of synthetic materials. Thromboembolism was a major problem. A variety of MONOCUSPID FLAP VALVES were evaluated including some made of stainless steel(97) ; a flexible monocusp Mylar valve with multiple hinges(98), and a Silastic valve(99). Similarly poor results were achieved with MULTICUSPID PROSTHETIC MITRAL VALVES made from Silastic(100), Teflon(101) or from polyurethrane(102). In order to try and overcome these poor results, PROSTHESES WITH ARTIFICIAL CHORDAE TENDINEAE were fashioned which aimed to mimic the normal mitral valve. Such prostheses, made from polyurethrane reinforced with Dacron(103), Dacron mesh infiltrated with fibroblasts(104) or Silastic(105), also yielded disappointing

results.

The first experimentally successful prosthetic BALL VALVE had a Lucite ball and a base made of Teflon(9). Despite survivals of up to 6 months, thrombosis and poor mechanical fixation were major problems. Ball valves were also constructed entirely of Lucite(106), Ivalon(107) or of steel(108). Starr(109,110) tried out many materials before selecting a prosthesis having a Silastic ball contained within a Lucite cage. A Silastic shield placed over the intracardiac sutures reduced the frequency of thrombosis(111). Cartwright et al.(112) used a double-caged valve made of titanium and Silastic.

CLINICAL RESULTS(112-114) :

MONOCUSPID VALVES : Ellis(116) used a monocuspid valve made of laminated Mylar covered with knitted Teflon. While the early results with this valve and its modifications were good, its use was discontinued due to late valve dysfunction. Malowney and Paton(99) used a monocuspid prosthesis made of Silastic.

MULTICUSPID VALVES : Silastic bicuspid valves were utilized by Long et al.(116) and by Young et al.(117). The latter prosthesis, which was more successful, had two flexible leaflets made of a silicone-coated Dacron fabric enclosed in a Lexan housing, which had an antithrombogenic covering layer.

VALVES WITH ARTIFICIAL CHORDAE TENDINEAE : A moulded polyurethrane valve with Teflon chordae tendineae was inserted into the mitral area of five patients(103). There were three operative deaths and the other patients survived 14 hours and 3 months respectively.

BALL VALVES : The introduction of the ball-valve prosthesis into clinical surgery by Starr(118) represents the greatest major recent advance in surgery for acquired valvular

disease(9). An early model of the Starr-Edwards prosthesis had a Silastic ball contained within a rigid cage made of Stellite 21 (Vitallium) and attached to a Teflon fabric sewing ring. In recent years a number of modifications have been made, mainly to try and obviate cloth wear. This aspect will be dealt with later in Chapter 2.

OPEN HEART PROCEDURES FOR AORTIC VALVE DISEASE

In 1956 Murray(62) reported the use of homograft aortic valve segments in the descending thoracic aorta. However, the incomplete relief obtained by using the Hufnagel valve in the descending thoracic aorta led cardiac surgeons to operate on the aortic valve itself. In 1958, Lillehei et al.(119) performed one of the first human cardiac valve replacements ever performed when they implanted a bicuspid silicone rubber flap-valve device in the sub-coronary position of a 56-year-old woman. The patient did well for 6 years before malfunction neccessitated replacement of the prosthesis. In 1959, Garamella et al.(120), Baird et al.(121) as well as Bailey and Zimmerman(63) treated aortic insufficiency by converting the tricuspid aortic valve into a bicuspid valve by excising or plicating the non-coronary cusp. This effectively narrowed the aortic valve ring. Attempts were also made to create a flap valve from the aortic wall just above the incompetent aortic valve. Others(64,122) sutured Ivalon to the free edge of one of the aortic cusps. In 1967, Hurley et al.(123) recommended open debridement of calcified material, plus commissurotomy for aortic stenosis. However, restenosis frequently occurred and many valves were too contracted and calcified to obtain significant haemodynamic improvement(4).

Following his work with a design engineer called W.C.Birtwell, Harken in 1960 was the first to successfully replace a diseased aortic valve with a prosthetic caged-ball valve in the natural position(65). He reported the survival of 2 out of seven patients with ball valves inserted in the

sub-coronary position for aortic incompetence. (In September of the same year Starr(118) accomplished a similar feat in a patient with mitral valve disease). Despite the encouraging initial results in dogs(124), the early caged-ball valves had a high incidence of thromboembolism ; they were noisy ; the silicone rubber balls were subject to deterioration, and there were high rates of paravalvular leakage and infection. Alterations in design were soon introduced. After the first successful mitral valve replacement with a Starr-Edwards prosthesis in 1960(118), this prosthesis soon gained wide acceptance and within 5 years thousands of Starr-Edwards prostheses had been implanted world-wide(9,125-129). The modern era of surgical replacement of diseased heart valves began at that time. The overall results were good and clinicians were able for the first time to compare the natural history of valvular heart disease with the effect of correcting an obstructed or leaking heart valve. Furthermore, a major advance in the understanding of valvular heart disease was achieved now that it was possible to separate valvular dysfunction from myocardial disability(4).

THE EVOLUTION OF CARDIAC SURGERY IN CAPE TOWN.

In 1942, Professor C.F.M. Saint, who was Professor of surgery at the University of Cape Town, ligated the patent ductus arteriosus in several patients. In 1949, Dr Walter L.Phillips was appointed to the newly created post of honorary thoracic surgeon at the Groote Schuur Hospital in Cape Town(130). Thoracic surgery was still in its infancy and his work consisted mainly of pulmonary surgery, ligation of a patent ductus arteriosus, excision of aortic coarctation and pericardiectomies. Later, Dr Phillips performed some of the first closed mitral valvotomies done in Cape Town.

However, many years were to pass before open-heart surgery

was to be performed in Cape Town. Following a period of training in cardiac surgery in America, Dr Christiaan N. Barnard returned to Groote Schuur Hospital's Department of Surgery bringing with him a heart-lung machine and the knowledge of how to use it safely. The first open-heart operation on the African continent was performed at Groote Schuur Hospital on July 28th,1958 by Drs Phillips and Barnard with Dr J.Ozinsky as the anaesthetist(131). The patient was a 15-year-old girl suffering from pulmonary valve stenosis.

Dr R.P. Hewitson acted as interim head of the Department of Cardio-Thoracic Surgery. Dr Barnard succeeded Dr Phillips as head of the Cardiothoracic Department. Supported by the excellent Cardiac Clinic built up by the late Professor Velva Schrire, an open-heart surgical unit of international standing was created. Valuable support was also provided to this end by such ancillary services as the Blood Transfusion Service, and the Departments of Chemical Pathology and Bacteriology. Once the cardiac surgical unit had been fully established, Dr Barnard was responsible for the development of several innovative surgical techniques(131) including e.g., a precursor of what is today known as the Mustard operation ; and the insertion of a tricuspid valve prosthesis to treat Ebstein's anomaly.

By 1962, (the same year that the Starr-Edwards caged-ball valve was introduced), the Cape Town cardiac surgical team had designed and produced a plastic tethered-plunger prosthetic heart valve, later known as the University of Cape Town (U.C.T.) prosthesis(132,133). Barnard and co-workers decided to eliminate a cage in their prosthetic design since they believed it could impinge on the ventricular wall and cause fatal arrhythmias. Problems with thromboembolism later led to the use of the U.C.T. prosthesis being discontinued.

COMMENT

From the chance stabbing of an Austrian labourer, which led Rehn to show that sutures could be placed in the living heart, to the modern speciality which can treat a wide range of cardiac disease is a germination without parallel in surgery. However, Moore(1) points out that despite the many achievements, the heart remains a central organ, acute post-operative disorders are poorly tolerated, and the mortality remains high in several types of cardiac operation. The patient pays a severe price for any technical error, be it valvular insufficiency due to failure of a single suture, hemiparesis due to dislodgement of a small thrombus, or a lethal arrhythmia from a poorly placed suture in the bundle of His. Like intra-cranial surgery, cardiac surgery has but a small "tolerance" for the careless, hurried or occasional operator.

CHAPTER 2.

STRUCTURAL DATA ON VARIOUS TYPES OF HEART VALVE PROSTHESES

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DESIGN CRITERIA FOR PROSTHETIC HEART VALVES(1,2)

For satisfactory long-term function in man, a prosthetic heart valve must fulfill numerous design criteria:

(i) It must be chemically inert and be compatible with human tissues. There should be an absence of a host reaction deleterious to the prosthesis.

(ii) The valve should cause little trauma to the formed elements of the blood.

(iii) It must have a low thrombogenicity. In third world countries a lack of need for anticoagulants is an advantage, as too, is a low price.

(iv) It should be durable enough to retain its physical and geometric properties over many years of function, bearing in mind that such a prosthesis has to open and close about 100,000 times a day(3). The valve should outlast the life-span of the patient.

(v) The prosthetic valve should present minimal obstruction to forward blood flow when open ; it should open and close quickly in response to changes in pressure gradients ; it should also be relatively competent in the closed position.

(vi) Permanent fixation in a physiological position must be technically feasible, safe, and secure over many years.

(vii) The valve should not annoy the patient by being noisy, and it should not require the patient to modify his lifestyle appreciably(4).

(viii) The valve should be resistant to infection.

A wide variety of heart valve prostheses have been designed in order to achieve these objectives. Illustrations of many models,some no longer in use, may be found in the literature(5-10). Silver and Wilson(11) illustrate some of the valvular prostheses that have been recently introduced.

Figures 2.1 to 2.3 summarize the process of heart valve development, the designs of currently used major categories of prostheses and the "rise and fall" in popularity of various valves.

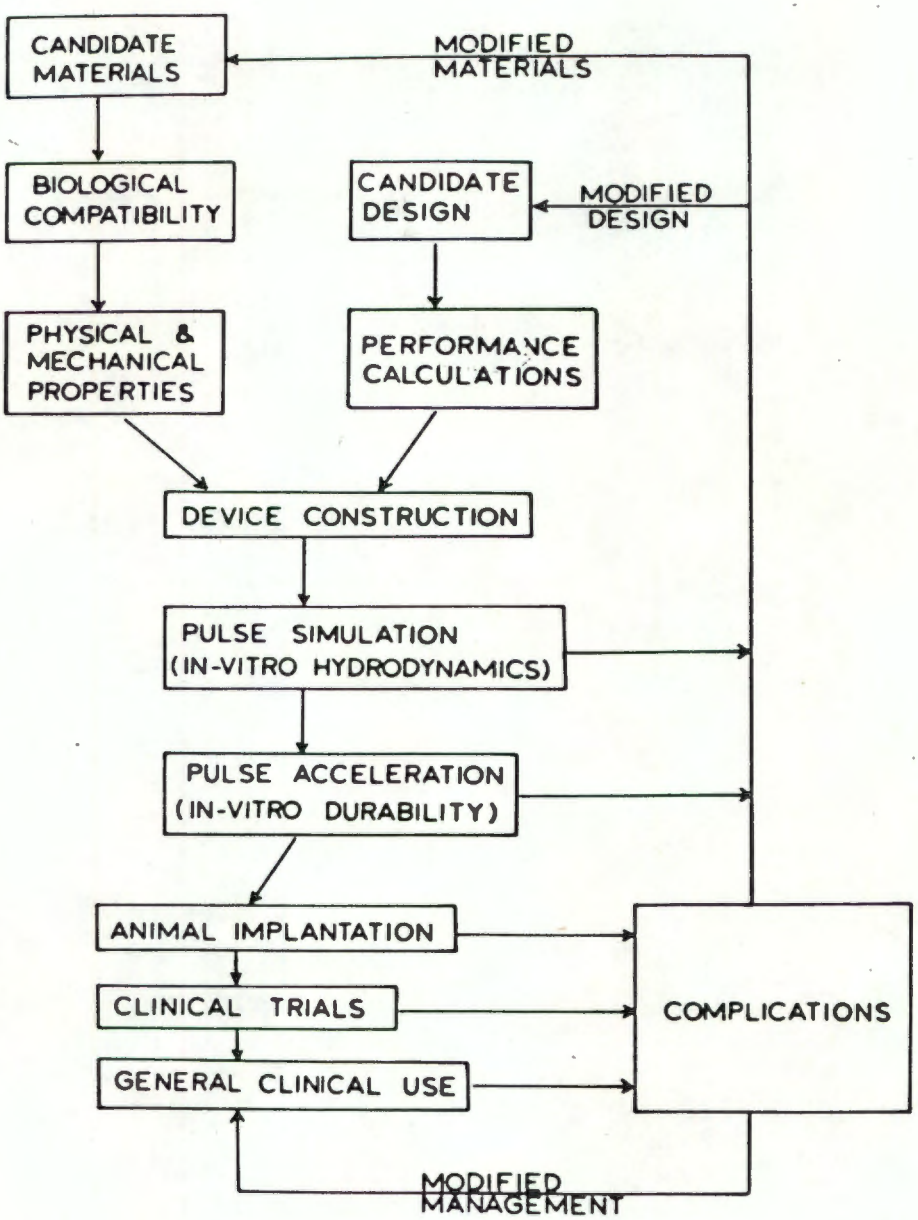


Figure 2.1 : Flow chart of heart valve development process. (Reproduced from Schoen, F.J., et al. : Ann. Biomed. Engin. 1982 ; 10 : 97).

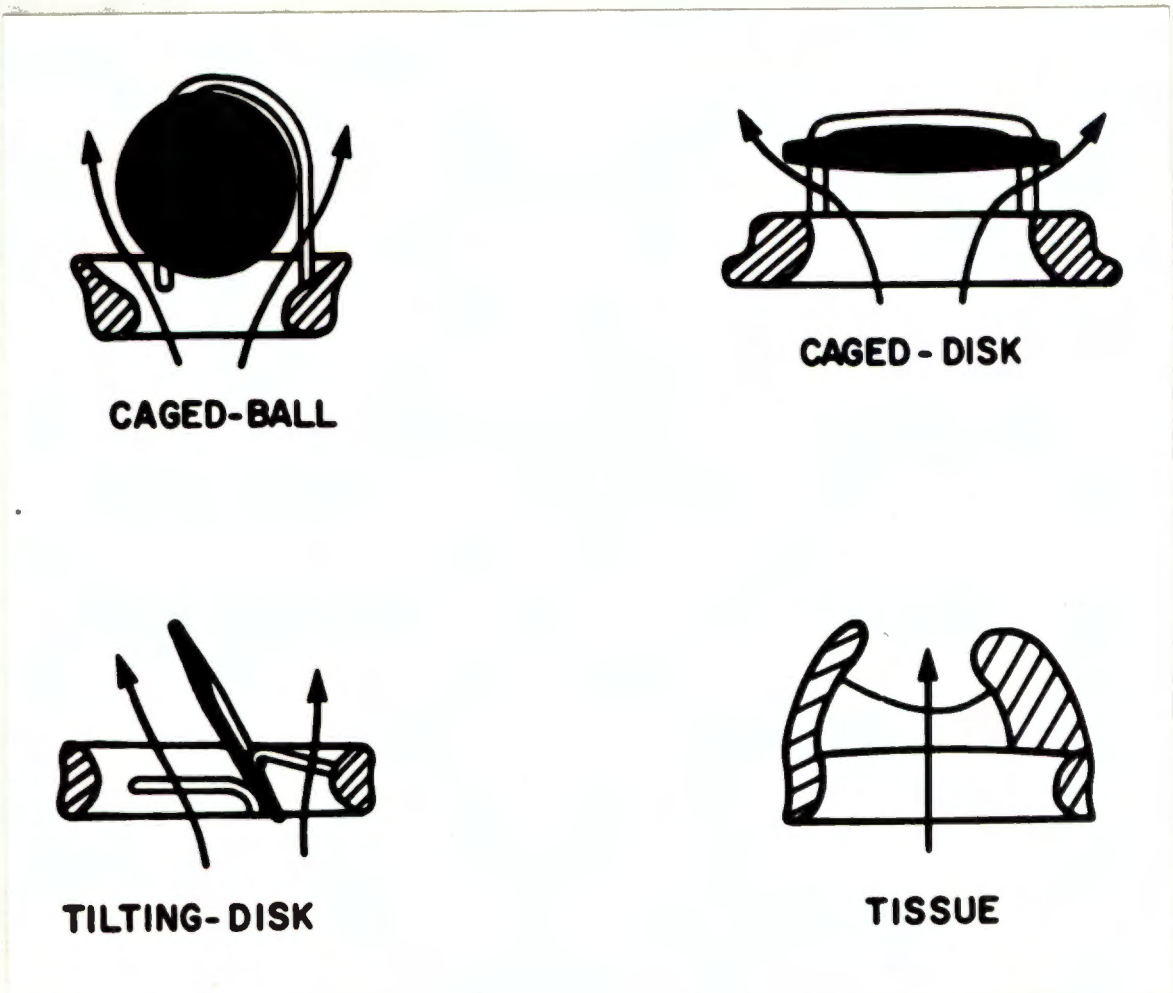


Figure 2.2 : Representative designs and flow patterns (schematic) of major categories of prosthetic heart valves. (Reproduced from Schoen, F.J., et al. : Ann. Biomed. Engin. 1982 ; 10 :97).

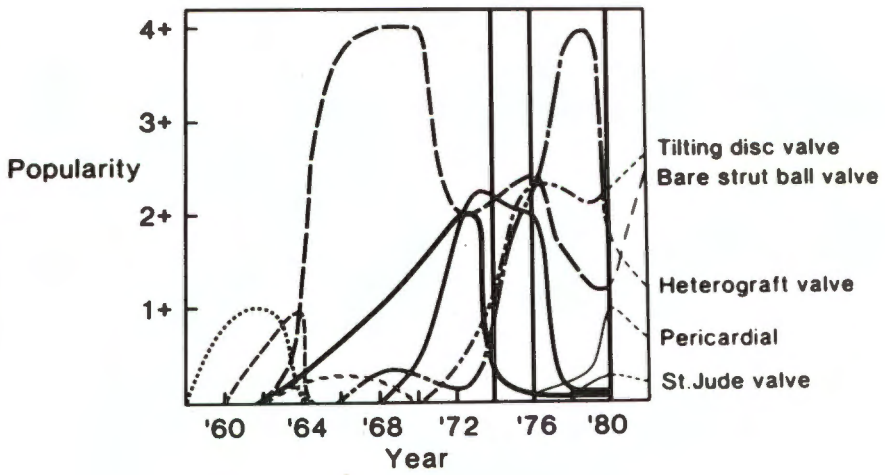


Figure 2.3 : The "rise and fall" in popularity of cardiac valvular prostheses over 2 decades. (Reproduced from McGoon, D.C. : Amer. J. Cardiol. 1982 ; 50 : 621).

The "Rise and Fall" of Replacement Valves

	Reason For	
Type of Valve	Introduction	Decline in Use
Cloth cusp	Hydrodynamic*	Failure in durability
Central disc	Hydrodynamic*	Failure in durability
Bare strut ball	Hydrodynamic*	Thrombogenicity†
Homograft	Less thrombogenic	Failure in durability; limited availability
Tilting disc	Hydrodynamic	Failure in "durability" ††; thrombogenicity†
Heterograft	Less thrombogenic	Failure in durability†
Cloth-covered ball valve	Less thrombogenic	Failure in durability; not less thrombogenic
Pericardial	Hydrodynamic	?Failure in durability†
Bileaflet	Hydrodynamic	?

* Compared with previously unreplaceable diseased valve. † Valve remains popular but would be even more successful without the limitation given. ‡ "Durability" in this usage refers to thrombotic immobilization of the disc.

TABLE 2.1 : CLASSIFICATION OF THE VARIOUS TYPES OF PROSTHETIC HEART VALVES

A.MECHANICAL PROSTHESES.

1.CAGED-BALL VALVES.

(i)Starr-Edwards ball valve.(*)
(ii)Smeloff-Cutter valve.
(iii)Harken valve.
(iv)Magovern-Cromie valve.
(v)Braunwald-Cutter valve.
(vi)DeBakey-Surgitool valve.

2.CAGED-DISC VALVES.

(i)Hufnagel-Conrad valve.
(ii)Cross-Jones valve.
(iii)Kay-Suzuki valve.
(iv)Harken-Cromie valve.
(v)University of Cape Town valve.(*)
(vi)Kay-Shiley valve.
(vii)Beall-Surgitool valve.
(viii)Starr-Edwards disc valve.
(ix)Cooley-Cutter valve.
(x)University of Stellenbosch valve.

3.HINGED-LEAFLET VALVE.

Gott-Daggett hinged-leaflet valve.

4.CAGELESS,CENTRAL-FLOW,LOW-PROFILE,TILTING DISC VALVES.

(i)Pierce valve.
(ii)Wada-Cutter valve.
(iii)Bjork-Shiley valve.(*)
(iv)Lillehei-Kaster valve.(*)
(v)Lillehei-Medical valve.
(vi)Hammersmith valve.
(vii)Hall-Kaster (Medtronic-Hall) valve.

(viii)Omniscience valve.
(ix)Omnicarbon valve.

5.BILEAFLET (BIVALVE) PROSTHESES.
(i)Kalke-Lillehei valve.
(ii)St. Jude Medical valve.(*)

B.TISSUE VALVES.

1.HOMOGRAFT AORTIC VALVES.
(i)Fresh homograft aortic valve.
(ii)Sterilized homograft aortic valve.

2.XENOGRAFT AORTIC VALVES.
(i)Unfixed xenograft valves
(ii)Formaldehyde-treated valve.
(iii)Glutaraldehyde-treated valves:
(a)Carpentier valve.
(b)Hancock valve(*).
(c)Carpentier-Edwards valve.(*)
(d)Angell-Shiley valve.

3.AUTOLOGOUS FASCIA LATA VALVE.(*)

4.DURA MATER HOMOGRAFT VALVE.

5.BOVINE PERICARDIAL XENOGRAFT VALVES.
(i)Ionescu-Shiley valve.(*)
(ii)Edwards Laboratory valve.
(iii)Mitroflow pericardial heart valve.(*)
(iv)Medox unicuspid pericardial heart valve.

6.POLYMERIC TRILEAFLET VALVE PROSTHESIS.
Abiomed heart valve prosthesis.

C.VALVE-CONTAINING CONDUITS.

1.Pulmonary artery and valve substitutes.

2.Left ventricle-to-aorta bypass.

3.Replacement of ascending aorta and aortic valve.

(*) INDICATES VALVES ENCOUNTERED IN THE PRESENT STUDY.

SURVEY OF THE VARIOUS TYPES OF HEART VALVE PROSTHESES :

A wide variety of heart valves have been implanted in patients worldwide. However, not all of these valves have been used clinically in each centre performing cardiac surgery. There are thus prominent regional differences in the utilization of the various prostheses. Table 2.1 gives a classification of most of the various types of prosthetic heart valves previously and currently available and lists most of the prostheses falling into each category. Prostheses which have been inserted in patients in Cape Town are indicated thus (*). The major advantages and disadvantages of prostheses which have not been used in Cape Town will be high-lighted.

STRUCTURAL DATA AND DIFFERENCES BETWEEN VARIOUS TYPES AND MODELS OF PROSTHETIC HEART VALVES (Tables 2.1 - 2.3) :

A.MECHANICAL PROSTHESES.

1.CAGED-BALL VALVES.

(i)STARR-EDWARDS PROSTHESIS :

The Starr-Edwards ball valve prosthesis has remained virtually unchanged in its basic design since its introduction in 1960, although numerous modifications have been made (Tables 2.2A - 2.2D). The initial Starr-Edwards prostheses (model 1000 aortic, 6000 mitral) had a Stellite-21 cage, a compression-moulded Silastic (silicone-rubber) poppet and a knitted Teflon (polytetrafluoroethylene) sewing ring. Stellite is an alloy composed of cobalt, chromium, molybdenum and nickel, which was earlier used in orthopaedic appliances.

Because of embolism and poppet shrinkage,the design was changed in 1965 so that cloth covered the valve seat (models 1260 aortic and 6120 mitral). This reduced thromboembolism and a modified curing technique greatly diminished deterioration

of the Silastic ball(12). In order to encourage endothelialization and so further reduce thrombosis, the entire cage was cloth-covered in the models 2300 aortic and 6300 mitral valves which were introduced in 1967. However,reduction of thromboembolism was at the cost of impaired hydraulic performance due to the smaller orifice size consequent to the cloth covering, as well as tissue ingrowth which was excessive in some patients.

The 2310-2320 aortic and the 6310-6320 mitral prostheses were characterized by protective metal studs on the inner aspect of the valve ring. These studs protruded through the covering cloth and protected the latter from the hollow Stellite-21 metal ball which was introduced in 1967. The change of the ball structure from Silastic to Stellite-21 was made in order to abolish the problem of ball variance. These prostheses had a larger orifice size and there was less risk of tissue ingrowth.Due to strut cloth wear the struts were lined by tracks made of Stellite-21 in the models 2400 aortic and 6400 mitral prostheses introduced in 1972.

It was not long before others introduced modifications to the Starr-Edwards prosthesis. Smeloff et al's valve(16) had a double cage. Harken's modification was a prosthesis having an open double titanium cage with a hollow silicone poppet and a Dacron skirt.(17).

TABLE 2.2A : DETAILS OF DIFFERENT MODELS OF STAR-EDWARDS BALL VALVE PROSTHESIS

MODEL	USED CLINICALLY	CAGE / STRUTS	SEWING RING COMPONENTS		BALL OCCLUDER (POPPET)	DIFFERENCE FROM PREVIOUS MODEL
			OUTER RING	INNER RING		
MITRAL PROSTHESES						
NON-CLOTH COVERED						
Lucite	In only 2 patients	Lucite, strut feet in orifice.	Teflon cloth	Lucite	Solid Silastic; seats proximal to its equator	
6000	1960	Closed cage; no feet in orifice. Stainless steel, then Stellite 21. Four struts joined at apex.	Knitted Teflon	Exposed metal on inflow aspect	Ditto. (Some with BA_2S04)	Stellite 21 cage MAIN PROBLEM: Thrombosis
EXTENDED CLOTH PROSTHESIS						
6120	1966	Closed cage; no feet in orifice. Stellite 21; 4 naked struts.	Teflon + Polypropylene cloth	Cloth covered inflow surface	Ditto	Cloth covers inflow aspect of ring. MAIN PROBLEM: Thrombosis

TABLE 2.2B : DETAILS OF DIFFERENT MODELS OF STAR-EDWARDS BALL VALVE PROSTHESIS (MITRAL PROSTHESES CONTINUED)

MODEL	USED CLINICALLY FROM	CAGE / STRUTS	SEWING RING COMPONENTS		BALL OCCLUDER (POPPET)	DIFFERENCE FROM PREVIOUS MODEL
			OUTER RING	INNER RING		
CLOTH-COVERED						
6300	1967	Closed cage; no feet in orifice. Stellite 21; 4-cloth covered struts not joined at the apex. Perforations in metal ring.	Teflon cloth	Teflon cloth	Hollow Stellite 21	Totally cloth-covered valve; metal ball. MAIN PROBLEM: Cloth wear on ring, poor haemodynamics.
6310	1968	Ditto	Ditto	Composite dacron cloth and studs.	Ditto; (Poppet seats close to the equator).	Studs in orifice.
6320	1970	Ditto; struts diverge slightly towards apex.	Ditto	Ditto	Ditto	Inner layer of Teflon and outer polypropylene. MAIN PROBLEM: Cloth wear on struts.
6400	1972	Ditto plus composite struts (metal liners and polypropylene cloth) which do not diverge towards the apex.	Teflon and polypropylene	Ditto	Solid Silastic	Metal tracks inside of struts. MAIN PROBLEM: Encourage neo-intima.
BEADED	1977	Stellite 21 with metal beads on non-contact areas.			Ditto	Metal beads on non-contact areas; Silastic ball.

TABLE 2.2C : DETAILS OF DIFFERENT MODELS OF STAR-EDWARDS BALL VALVE PROSTHESIS

MODEL	USED CLINICALLY FROM	CAGE / STRUTS	SEWING RING COMPONENTS		BALL OCCLUDER (POPPET)	DIFFERENCE FROM PREVIOUS MODEL
			OUTER RING	INNER RING		
AORTIC PROSTHESES						
NON-CLOTH COVERED						
Pre-1000	Early 1960's	Stainless steel cage; 4 struts	Teflon and polypropylene	Stellite 21	Solid Silastic	
1000	1962	Stellite 21 cage; 3 struts joined at apex.	Ditto	Ditto	Ditto	3 struts; foam in sewing ring. BA_2SO_4 in some poppets. MAIN PROBLEM: Ball variance.
1200	1965	Ditto; tapered support at each strut junction.	Ditto	Ditto	Ditto	No feet in orifice; Spherical seat made convex, reduced poppet stroke distance. BA_2SO4 in some popets. Modified curing technique.
1260	1968	Ditto	Ditto	Ditto	Solid Silastic	Scalloped outflow metal ring. All poppets contained BA_2SO4. MAIN PROBLEM: Thrombosis

TABLE 2.2D : DETAILS OF DIFFERENT MODELS OF STAR-EDWARDS BALL VALVE PROSTHESIS : AORTIC PROSTHESES : CLOTH-COVERED

MODEL	USED CLINICALLY FROM	CAGE / STRUTS	SEWING RING COMPONENTS		BALL OCCLUDER (POPPET)	DIFFERENCE FROM PREVIOUS MODEL
			OUTER RING	INNER RING		
2300	1967	Stellite 21 cage; three struts joined at apex. Tapered support at each strut junction.			Hollow Stellite 21	Totally Teflon covered orifice, double layers of Dacron (later Teflon) on struts. MAIN PROBLEMS: Poor haemodynamics and cloth wear.
	1968 Close tolerance. 1970 Wider tolerance.	2 models: first had low clearance and second intermediate clearance between ball and cage. A perforated metal ring. Three thin struts joined at apex after 12/69. Struts more divergent at apex.	Teflon and polypropylene	Composite Dacron cloth & studs	Solid Silastic	Struts covered by inner Teflon and outer polypropylene. MAIN PROBLEM: Sticking ball in open position.
2320	1970	Struts covered by inner Teflon and outer polyproplene.	Ditto	Ditto	Ditto	MAIN PROBLEM: Strut cloth wear.
2400	1972	Composite struts covered with polypropylene fabric and Stellite 21 tracks.	Compressible	Ditto	Ditto	Stellite tracks inside struts.
BEADED METAL	1974	Same as mitral prosthesis (see Table 2.2B)				

Lucite = methyl methacrylate.
Stellite 21 = alloy of cobalt, chromium, molybdenum and nickel.
Teflon** = polytetraflourethylene.
Dacron** = polyester.
Silastic* = silicone rubber
* Dowcorning
** Dupont

TABLE 2.3: DETAILS OF OTHER BALL VALVE PROSTHESES (EXCLUDING STARR-EDWARDS PROSTHESES).

VALVE	USED CLINICALLY FROM	CAGE / STRUTS	SEWING RING	BALL OCCLUDER (POPPET)	MAJOR PROBLEMS
Harken	1960	Early: Inner & outer cages with eight struts. Later: Three cloth-covered struts with plastic linings inside ring. Closed cage.	Ivalon sponge	Hollow Stellite; seats proximal to its equator.	Thromboembolism
Magovern-Cromie	1962	Titanium open cage. Automatic vixation mechanism.	No sewing ring: Models A1,A2,A3 up to 1968. Dacron on sides and part of base from 1968. (Model A4).	Silicone rubber with barium sulphate.	Paravalvular leaks. Thromboembolism.
Smeloff-Cutter	1964	Titanium bare strutted open ended double cage.	Convex metal inner ring.	Silicone rubber.	Ball swelling due to lipid absorption. Open cage attached to ventricular septum.
Braunwald-Cutter	1968	Single,open cage,Dacron cloth-covered struts.	Polypropylene cloth over orifice	Radiolucent Silicone rubber.	Thromboembolism,variance, haemolysis, apical cloth wear, paravalvular leaks.
De Bakey-Surgitool	1969	Closed cage,no feet in orifice, 3 bare titanium struts (recently coated with pyrolytic carbon).	Plastic (polyethylene) inner ring. Serrated metal ring.	Radiolucent poppet. (Recently pyrolite ball).	Strut wear.

(ii)SMELOFF-CUTTER VALVE(18) :

This full-orifice (non-overlapping) caged-ball prosthesis was developed during the early 1960s by Drs Smeloff, Cartwright, Davey and Kaufman(19-21). The Smeloff-Cutter valve prosthesis (Table 2.3) is machined from a single piece of pure titanium. The orifice and struts are bare metal. The two cages each have 3 struts, which are not continuous across the ring. The full orifice design aims to reduce thromboembolism by a washing effect produced by regurgitation of blood around the ball. The one cage is shorter than the other. In the mitral position the poppet occupies less of the left ventricular cavity than is the case with the Starr-Edwards prosthesis,because the poppet rests partially in the left atrium in systole. This is an advantage if the left ventricle is not dilated,as there is less chance of the valve causing left ventricular outflow tract obstruction. Because of its full-orifice design, the Smeloff-Cutter valve, when used in the aortic position, allows a larger prosthetic orifice than is possible with a conventional ball valve.

Design-related complications included ball swelling due to lipid absorption which was corrected in 1966 by altering the curing process ; rarely the tip of a metal strut (open-ended cages) perforated the endocardium or became entangled in a papillary muscle remnant(22). Cardiac catheterization studies failed to show the improved haemodynamics expected of the full-orifice prosthesis(23-27). Diastolic pressure gradients across the mitral prosthesis of 5mm Hg at rest and 10-12mm Hg during exercise are not dissimilar to those of most other prosthetic heart valves. With the use of anticoagulants average thromboembolic rates of 3% per year after aortic valve replacement(25,28) and 6% per year after mitral valve replacement were achieved(18). These results are not dissimilar to those of other noncloth-covered prostheses. The Smeloff-Cutter valve has the advantage over disc prostheses of a very low incidence of thrombotic stenosis(18). However, Smeloff et al.(29) in 1982 reported the development of a fibrous subvalvular pannus, which was the cause of mitral stenosis in 16 of 376 patients with this prosthesis. Although

the design has not been significantly altered in over 17 years, this finding has prompted Smeloff et al. to examine some design alterations in the laboratory and in implantation[2] in dogs.

(iii)HARKEN VALVE.

Dwight Harken and co-workers successfully implanted a caged-ball prosthesis in the aortic root of human patients in the early 1960s, but the initial operative mortality was 71%.(30,31). The early Harken valve incorporated both inner and outer cages with a total of eight struts. The outer cage had the function of preventing the aortic wall from interfering with movement of the poppet(18).The valve was constructed so that it could be firmly anchored by Surgaloy (American Cyanamid Co.) and covered by silk sutures in Ivalon (Clay-Adams Inc.) or Teflon backing.

The modern model of the Harken caged-ball prosthesis has a hollow metal (Stellite) ball enclosed by three cloth-covered struts. A plastic (polyethylene) inner ring seats the poppet proximal to its equator.

(iv)MAGOVERN-CROMIE VALVE.

This sutureless heart valve(32) was developed by Dr George Magovern of the University of Pittsburgh School of Medicine and Mr Harry Cromie, a machinist. (This successful venture led Cromie to start a company called Surgitool,Inc. which produced the Magovern-Cromie, DeBakey, Beall and Harken prostheses)(18).

The initial Magovern-Cromie valve had a stainless steel closed cage surrounding a silicone rubber ball. The valve base incorporated curved metal pins which were turned outward and through the aorta when the cage was rotated horizontally with a special instrument.

When autopsy revealed thrombus at the apex of the cage of

this prototype valve, all subsequent valves were made with an open-ended cage. Model A1 introduced in 1963 had 24 pins attached to an upper metal plate and 24 additional interdigitating pins projected from the lower rim. Model A2 of 1964(33) had a silicone rubber flange over the outflow aspect of the ring to limit periprosthetic leaks. The poppet contained barium sulphate for radio-opacity. Model A3 was introduced in 1965 due to the problem of thromboembolism with the earlier model. Model A3 had the rubber flange replaced by a cuff of Dacron cloth and its inflow surface was partially covered with Teflon. Model A4 introduced in 1968, had a Dacron fabric cover over most of the base of the titanium prosthesis, but the struts were bare. In this model only the aortic valve used the sutureless technique and the mitral prosthesis was abandoned.

Although the sides and part of the base of the Magovern-Cromie prosthesis were covered by Dacron in 1968, a large amount of bare metal remained in the sutureless prosthesis. Thus, the cloth did not extend to the edge of the inflow surface, but spared a metal rim and three metal projections(18). The rotating pin fixation mechanism resulted in a large amount of metal within the valve orifice. The establishment of safe techniques for cardiopulmonary bypass and myocardial protection rendered the rapidly implantable sutureless Magovern-Cromie valve redundant. Its use was discontinued in the late 1960s.

(v)BRAUNWALD-CUTTER VALVE.

As a result of Braunwald and Morrow's observations that fabric leaflet valves become covered by host tissue(34), Braunwald reasoned that porous cloth coverings could be beneficially applied to mechanical prostheses in order to combine the advantages of both devices. She and her colleagues modified several current noncloth-covered (Starr-Edwards, Cross-Jones, Kay-Shiley) prostheses by covering the struts

with loosely knit polypropylene and the metal ring with stretch-knit Dacron(35,36) : Experimental work with these modified prostheses yielded the following information(18,37,38) :

1. The fabric covering the metal increases thrombogenicity of the prosthesis, but the more adherent thrombus gets covered by endothelial cells, thereby producing a non-thrombogenic autologous surface.
2. Thicker thrombi take a longer time to undergo organization.
3. The thrombus which forms is seldom more than twice as thick as the underlying cloth.
4. A coarse fibre weave in the cloth favours a uniform fibroblast infiltration of the thrombotic layer and results in better adherence.
5. Thicker tissue layers more often undergo degeneration and give rise to emboli.This may be related to the poor vascularization of this layer.
6. Anticoagulants promote the formation of a thinner, more uniform thrombus-tissue layer.
7. The cloth covering the struts had an abrasive action which led to wear of soft poppets (e.g., those made from silicone rubber), whereas hard poppets (made of Stellite) resulted instead in wear of the cloth(39).

In 1967 Braunwald and co-workers started clinically to use standard, noncloth-covered Starr-Edwards prostheses which they had completely covered with cloth. An encouragingly low incidence of thromboembolism was noted, but the platelet-fibrin layer developed slowly in humans (unlike the experimental results in calves) and the human neo-intima was thin and delicate. An important additional disadvantage was that the cloth covering the ring rendered the smaller prostheses stenotic(40). In order to overcome the latter difficulty, the Braunwald-Cutter totally cloth-covered prosthetic heart valve was produced by Cutter Laboratories. The Braunwald-Cutter caged-ball valve(41) had a titanium frame

with an open-ended cage. The ring was covered by polypropylene mesh and the struts with knitted Dacron. The mild-cure silicone rubber poppet was similar to that used in 1966 in the Smeloff-Cutter valve.

(vi)DEBAKEY-SURGITOOL AORTIC VALVE.

This prosthesis was designed by Dr Michael E.DeBakey and associates of Baylor College of Medicine, Houston, Texas and Mr H.Cromie of Surgitool,Inc. The aim was to devise a prosthesis which would not be plagued by the problem of ball variance that was encountered with the early model Starr-Edwards aortic valves. Several different models were manufactured in the evolution of this prosthesis.

The first DeBakey-Surgitool valve had a titanium poppet and the struts plus the ring were covered with Dacron velour. This totally cloth-covered design was unsuccessful due to severe haemolysis(42). The second model of the valve had a pyrolytic carbon-silicone alloy coated ball with a bare titanium cage(43). The poppet was rendered radio-opaque by an inner tungsten screen. The fabric sewing ring was designed for aortic valve replacement only(18). The third model of the DeBakey-Surgitool valve (introduced in 1969) had a primary orifice covered with a double layer of woven Dacron. Severe haemolysis prohibited its use. The fourth model introduced in 1971 was characterized by a base ring made of ultrahigh molecular weight polyethylene. This substance was not ideal since it could only be sterilized by gaseous methods and steam autoclaving could not be used. The fifth valve design (available from 1972) had a base ring made of pyrolytic carbon(18).

There have been very few reports published of results using the DeBakey-Surgitool valve(44,45). Embolism appears to have been on a par with other noncloth-covered prostheses. One problem peculiar to this prosthesis has been wear and/or fracture of the struts due to the combination of an extremely

hard pyrolytic carbon ball and a soft titanium cage(46). Design alterations in the mid-1960s by Cutter Laboratories virtually eliminated ball variance with silicone rubber poppets(18). The long-term durability of such poppets has still to be proved.

DEBAKEY-SURGITOOL MITRAL VALVE:

This prosthesis has been used at Baylor College by DeBakey and co-workers for several years, but it has not been made available for general use. Like the Beall-Surgitool valve it has a pyrolytic carbon disc and Dacron velour covers the orifice. The struts cross on the DeBakey valve, unlike the parrallel arrangement of the Beall valve.

2.CAGED-DISC VALVES.

The caged-ball design gained worldwide acceptance following early successes with mitral valve replacement in 1960(18,47). In those early years there was difficulty in distinguishing between valve-related and patient-related complications. There was concern as to whether caged-ball valves could produce subaortic outflow tract obstruction (low cardiac output) or whether ventricular fibrillation might result from septal irritation by the cage. Pathological specimens at times gave support for such a possibility(48,49). This concern regarding the suitability of caged-ball valves for mitral valve replacement in patients with non-dilated left ventricles led to the development of numerous low-profile prostheses in the mid-1960s. The chief advantage of this type of valve is that the retaining cage is much shorter, and thus lower in profile, than in the ball valve. These caged disc valves had a lateral flow design.

(i) HUFNAGEL-CONRAD VALVE(50).

Drs Hufnagel and Conrad of the Georgetown University Hospital described a polypropylene and silicone rubber caged-disc prosthesis.

Hufnagel also evaluated a stemmed disc-type valve. Various shapes of disc were tried out, but this valve and its numerous modifications were not satisfactory in a blood medium. Its use was soon abandoned due to problems of wear and thrombosis.

(ii) CROSS-JONES VALVE(51).

This prosthesis had an open-ended cage composed of 3 struts and there was a radiolucent poppet which contained a radio-opaque ring. There were no feet within the valve orifice. Significant complications included thromboemboli, cocking of the disc and disc variance.

(iii) KAY-SUZUKI VALVE(49).

This valve was designed by Drs Earle B. Kay and Akio Suzuki. It had a closed-ended cage composed of 4 struts. There were also 4 short, open base feet which projected into the orifice opposite the cage. The valve also had a double-ring valve base (metal inner ring) and a radiolucent poppet. Major problems were thromboemboli and disc variance.

(iv) HARKEN-CROMIE VALVE(52).

This has a closed cage formed of 4 thin, crossing struts and a radio-opaque poppet. Thromboemboli and disc variance were recognized complications.

(v) UNIVERSITY OF CAPE TOWN VALVE(53,54).

This locally developed tethered-plunger prosthesis had flat (lenticular) and cone-shaped Silastic poppets. The U.C.T. mitral valve prosthesis initially had a plump lenticular disc suspended from a T-piece which moved up and down through a ring at the end of a suspension arm. In the mitral prosthesis the restraining mechanism was placed in the atrium and thus overcame the most important disadvantage of the ball-valve. The suspension arm was anchored to a larger steel ring which formed the valve seat. This seat ring was covered with Ivalon, and later with Teflon, which also acted as a sewing ring. Later the poppet was modified into a slimmer lenticular outline. The U.C.T. (lancer) aortic valve(55) had two rings and two suspension arms to hold the I-pieces of the double cone-shaped poppet. Problems with thromboembolism later led to the use of the U.C.T. prosthesis being discontinued.

(vi)KAY-SHILEY VALVE.(56,57).

The Type I Kay-Shiley valve had 4 struts which projected vertically from the Stellite sewing ring to form 2 bars made of bare metal (Stellite). The closed cage held a radiolucent silicone rubber disc. This valve was used for mitral and tricuspid valvular replacements(58,59). The Type II valve was produced in response to a high thromboembolic rate and the modification consisted of extending the knitted Teflon cloth to reduce the orificial bare metal(60). The Type III Kay-Shiley valve had a muscle guard projecting from the ring of the valve to protect the excursion pathway of the disc from encroachment by adjacent myocardium. It has been pointed out that this modification nullifies the originally stated theoretical advantage of the low-profile valve, namely that it avoids contact with the myocardium(61). The addition of a second guard gave rise to the Type IV valve, which also substituted Delrin for silicone rubber as the disc

material(62).

Since low profile prostheses should produce less obstruction of the tertiary orifice (the space between the poppet and the aortic wall), Bjork implanted the Kay-Shiley valve in the aortic position in 60 consecutive patients. Post-operatively the average systolic gradient was disappointing : 27 mm Hg at rest and 38 mm Hg during exercise(63).

Major complications encountered with the Kay-Shiley prosthesis included thromboembolism, sudden unexpected unexplained death, grooving and disc wear, restenosis with tissue ingrowth, perivalvular leaks, disc cocking and disc variance(6). According to Lefrak and Starr(18) the established vulnerability of the Kay-Shiley prosthesis to catastrophic malfunction is typical of disc prostheses ; a small amount of thrombus may critically interfere with disc mobility, rendering it stenotic and susceptible to a vicious cycle of rapidly progressive thrombosis. Deaths from low cardiac output syndrome or arrythmias continue to occur despite the use of low-profile valves.

(vii) BEALL-SURGITOOL VALVE.

Dr Arthur Beall and the staff of Surgitool Inc. produced a partially cloth-covered, low-profile valve which they hoped would have a lower risk of thromboembolic complications. The disc consisted of extruded Teflon and the titanium struts were covered with solid Teflon(64). Due to premature disc wear(65,66) the disc was changed to a thicker, compression-moulded Teflon disc in Model 103. The next alteration to the prosthesis was in response to reports of poor hemodynamic responses during exercise(67). In the Model 104 Beall prosthesis the primary and secondary orifice areas of the paediatric and small-sized valves were enlarged.During the ensuing years it became apparent that disc wear, particularly of the edge of the disc, was still a significant

problem(68-71). Disc wear manifested clinically as increased hemolysis and mitral incompetence or stenosis. Model 105 introduced in 1971 no longer had a Teflon disc and there was no Teflon on the struts. A pyrolytic carbon-silicone alloy coated the new graphite disc and the titanium wire struts(43). However,Model 105 was plagued by the problem of strut fracture due to cracking of the brittle carbon alloy(72,73).

In Model 106 the diameter of the strut wire was increased from 0.030 to 0.045 inches and it was packaged more strongly for shipping and sterilization(18). The degree of hemolysis associated with the Beall-Surgitool valve is greater than that seen with the noncloth-covered caged-ball or tilting disc valves. The increased hemolysis is probably related to the Beall-Surgitool valve's combination of an overlapping disc with a Dacron velour cloth-covered orifice. The prosthesis has also failed to reduce the incidence of thromboembolism after mitral valve replacement.

(viii) STARR-EDWARDS DISC VALVE.

The first Starr-Edwards disc valve had a poppet made of hollow Stellite 21 and the cage was made from the same metal alloy(74). The heat-tempered poppet was made harder than the cage legs, which were made thick enough to prevent problems due to wear. The sewing ring was made of Teflon cloth. While the problem of disc edge wear was eliminated by this valve model, it later became evident that thromboembolism, poor hydraulic function and thrombotic entrapment of the disc were significant problems(18,75,76). In the Model 6520 Starr-Edwards disc prosthesis(77) the disc was made from Hifax (ultrahigh molecular weight polyethylene). It contained a radio-opaque titanium ring. The hydraulics were improved by enlargement of both the primary and secondary orifices. The same closed cage design of Stellite 21 as the previous design was used in this new model.

Up till 1979, Edwards Laboratories had not been notified of a single case of disc wear, strut fracture, or poppet embolization with either the 6500 or 6520 Models. In common with other disc valves it shares an haemodynamic effect inferior to caged-ball or tilting disc valves, and a tendency to disc immobilization by thrombus or endocardium. It also has a similar embolic rate to other noncloth-covered valves(18).

(ix) COOLEY-CUTTER VALVE.

Dr Denton Cooley's experience with prosthetic valve construction began during his association with Dr D. Liotta at the Baylor College of Medicine in the mid-1960s(18). Liotta's eccentrically hinged disc valve closed too slowly allowing an unacceptable amount of incompetence(78). This was followed by the Cooley-Liotta-Cromie prosthesis, which was a modification of the Starr-Edwards valve. It had a titanium ball and Dacron velour completely covered the ring and the struts(79). Its use was soon discontinued due to cloth wear and haemolysis(80). The Cooley-Bloodwell-Cutter prosthesis introduced in 1966 had a silicone-rubber disc and bare titanium cage legs. The orifice of the valve was covered with Dacron cloth(81). Thromboembolism(82) and disc wear soon led to its use being discontinued.

The COOLEY-CUTTER VALVE(83) introduced in 1971 had a double cage made of titanium struts. It had a peripheral,self-washing regurgitant stream in the closed position and the knitted Teflon sewing ring was eccentric in order to reduce the danger of poppet entrapment by mural endocardium. Initially the valve was a mitral prosthesis only, but in 1973 an aortic prosthesis with a biconical occluder was introduced. In the same year the mitral poppet was changed to this type too.

Like the DeBakey-Surgitool and the Lillehei-Kaster prostheses, the Cooley-Cutter valve has a hard pyrolytic carbon poppet and relatively soft titanium struts. Titanium

strut wear has been reported with the DeBakey-Surgitool valve and the Cooley-Cutter valve may have the potential for similar wear. Strut fracture of the Cooley-Cutter prosthesis has been reported(84,85).

(x) UNIVERSITY OF STELLENBOSCH VALVE.

The University of Stellenbosch mitral valve prosthesis was developed by Dr Pieter M. Barnard and colleagues at the Karl Bremer Hospital and the University of Stellenbosch, South Africa. The Silastic (silicone rubber) disc (manufactured by the Dow-Corning Center for Aid to Medical Research, Michigan, U.S.A.) was enclosed in an open-ended, stainless steel cage having 4 bare metal struts. The original disc incorporated a stainless steel ring which was later changed for a perforated nylon plate. Electron beam-welding of the prosthesis was performed by the Technical Department of the South African Council for Scientific and Industrial Research. The sewing ring of the prosthesis was covered with Dacron velour. Following on testing of the valve in baboons(86), clinical use of the prosthesis started in July 1967. In 1970 Barnard et al.(87) reported their clinical experience with 25 patients in whom the valve had been implanted. Thirty-percent of patients showed early thromboembolism (none fatal) and 9% had late embolism. In contrast to other reported series(40,88), the cloth covering (Dacron velour) on the University of Stellenbosch mitral valve prosthesis did not reduce the incidence of early embolism. Due to the high rate of thromboembolism, this valve is no longer used.

3. HINGED-LEAFLET VALVE.

In the mid-1960s Dr V.L. Gott and colleagues devised a hinged-leaflet, low-profile valve(89,90) for aortic valve replacement. The Gott-Daggett valve had a central cross strut with multiple prongs projecting from the inner aspect of the

ring. The leaflets were radiolucent. Major problems with this prosthesis were thromboembolism and haemolysis. The latter was associated with an increased incidence of gallstones(6,91).

4.CAGELESS,CENTRAL FLOW,TILTING DISC,LOW-PROFILE VALVES.

(i) PIERCE VALVE.

This valve was the earliest tilting disc prosthesis devised(92). The standard sewing ring attached by Edwards Laboratories was cloth-covered and plastic composed the inner portion of the ring. The ends of the spindle supporting the tilting disc were retained by this plastic inner ring. The valve was used in experimental animals at the National Heart and Lung Institute, U.S.A. It was shown that laminar flow occurred through the larger orifice,but the lesser orifice had a turbulent flow pattern. In vivo it was found that a small amount of thrombus or granulation tissue could seriously interfere with valve function.

(ii) WADA-CUTTER VALVE.

This valve was jointly developed by Dr Juro Wada and Cutter Laboratories. The valve has no obvious cage. Two small metal feet project horizontally into the valve orifice, producing a hinge upon which the disc pivots. The titanium inner ring extends as a lip onto the outflow and inflow surfaces. The base ring has two notches. The radiolucent solid Teflon (polyethylene) disc is vaguely Z-shaped in profile and it occludes the orifice by having part of the disc seating on both surfaces. The larger portion of the disc seats on the outflow side of the titanium ring. The smaller portion of the disc overlaps onto the inflow side of the ring. The disc tilts open to an angle of 75 to 80 degrees. The valve was used in the mitral, tricuspid and aortic positions. Problems

encountered included early disc wear(93), total valve thrombosis(94), thromboembolism and peribasilar leaks with notable regurgitation(6). These complications, as well as instances of fatal poppet embolization, led to this prosthesis being abandoned.

(iii) BJORK-SHILEY VALVE.

Encouraged by the designs of both the Pierce and the Wada-Cutter valves, Dr Viking O. Bjork of the Karolinska Institute in Sweden combined with Mr Donald Shiley to develop the Bjork-Shiley prosthetic valve. (Shiley had previously worked with Mr Edwards on the Starr-Edwards valve before forming his own company, Shiley Laboratories, Inc., in Santa Ana, California).

The valve devised by Shiley was tested experimentally in 1968 and clinical usage was instituted in 1969(95,96). The valve has 2 curved, roughly U-shaped, naked cast Stellite struts which are heat-fused to the ring. They are bent apart for insertion of the disc. The latter is held in place by fitting the outflow strut into a central depression on the disc. Delrin was initially used to construct the disc, but it absorbed moisture during steam autoclaving with resultant swelling of the poppet(97). Thus, in 1971 the disc material was changed to graphite coated with pyrolytic carbon, and the edge was made thicker(98). The disc tilts open to 60 degrees and does not overlap the valve ring on closure. This allows a degree of regurgitant flow through the closed valve (10% versus 3% for the Starr-Edwards valve) in order to prevent and to wash the valve free of thrombi. Such a construction permits an optimal orifice diameter and area for a given tissue diameter ; it provides a low resistance to blood flow and is less traumatic to erythrocytes with minimal incompetence(99). Initially, in the mitral prosthesis the disc was designed to open only to 50 degrees in order to avoid its touching the ventricular endocardium. Later the angle was changed to 60

degrees to improve post-operative haemodynamics and to better wash the ventricular side of the disc during diastole(100). Turning of the disc in vivo was expected to prolong the life of the disc. From late 1975 a radiopaque tantalum foil loop marker was incorporated into the disc to assist in diagnosis of thrombosis(100a,100b).

There is no fabric on the struts or on the primary orifice. The aortic prosthesis has a vertical, thin-walled base and a rectangular sewing ring, which serve to give a greater internal orifice in relation to the valve's external diameter. The mitral valve has a more horizontal, L-shaped sewing ring in profile. Despite the theoretical advantage of the absence of a central occluder in the Bjork-Shiley valve, it has been shown that the flow pattern through the valve is primarily through the major orifice and not through the entire internal orifice. Also the flow pattern is directed laterally and not centrally as in natural valves or with bioprostheses(18,101).

The Bjork-Shiley valve may be easily implanted in the aortic root and its low profile makes coronary arterial re-implantation into a Dacron graft easier. Durability has been very good and strut fracture is rare. The thin, unpadded sewing ring makes peri-prosthetic leakage in a rigid aortic root more likely. The fundamental weakness of the tilting disc design is the close association between the mobile poppet and the thrombogenic valve ring(18). Thrombus on the ring can easily interfere with poppet motion. Such failure is often sudden and catastrophic. In an attempt to reduce the area of flow stagnation predisposing to thrombosis on the outflow side of the disc, the design was later altered so that the disc now had a convexo-concavo outline and the pivot point was moved 2.5 mm downstream to reduce obstruction by thrombus which might form(102).

Later a Bjork-Shiley prosthesis which had a 70 degree opening angle was introduced. However, strut fracture led to this concavo-convex Bjork-Shiley 70 degree opening valve being

withdrawn from the market (F.C. Marcus & Co. Ltd., South africa, personal communication). In 1983, a new type of monostrut Bjork-Shiley valve was introduced. No welding is present ; the inlet and outlet struts are all part of the same metal since the valve is machined from a solid piece of cobalt alloy. The product name "monostrut" refers to the valve's outlet strut which is now a single projecting finger of metal, rather than the U-shape associated with the concavo-convex valves. This new strut has a cross-sectional area 3.5 times greater than the old wire outlet strut. The disc occluder opens to 70 degrees and is made of pyrolytic carbon.

(iv) LILLEHEI-KASTER VALVE.

Dr C. Walton Lillehei and colleagues performed one of the first human heart valve replacements ever attempted using a bicuspid silicone rubber flap-valve aortic prosthesis(103). An electrical engineer called Robert Kaster working in Lillehei's laboratory tried to design an improved heart valve prosthesis. He and Dr A. Cruz produced the CRUZ-KASTER pivoting disc valve which had a concavo-convex (meniscus) shaped disc that tilted open to up to 80-85 degrees. However, blood flowed only on one side of the disc, predisposing to thrombosis on the other side. It was tested experimentally from 1963, but was never used clinically(104). In 1965, the pivotal axis was moved towards the centre, so allowing blood flow on both aspects of the disc. The struts were altered and then abolished, yielding a cageless design with lateral guides to hold the disc in place(105). The poppet was still a pivoting disc, but it was inclined at 18 degrees when closed to aid rapid opening and closing.

The LILLEHEI-KASTER valve evolved from the above valve after evaluation of various materials. Delrin (acetal homopolymer) and various plastic discs were found to wear(106). The valve was used clinically for the first time in 1970 by Dr Lillehei(107) and was made commercially available

the following year.

The Lillehei-Kaster(1,6,18) valve prosthesis has a pivoting disc composed of a graphite centre covered by a thin layer (250 um) of a carbon-silicone alloy (Pyrolite ; Gulf General Atomic, Inc., San Diego, California). The pyrolytic carbon disc is retained by a titanium housing that allows the disc to open to a maximum angle of 80 degrees from its closed position of 18 degrees to the horizontal (62 degrees of movement). The disc seats in the prosthesis lumen at its equator. The metal housing can be rotated within the Teflon cloth sewing ring to permit optimal alignment of the disc after sewing ring fixation(1). The effective diameter of the valve orifice is smaller than the diameter of the disc. The inner ring consists of bare metal(9).

Two naked (titanium) metal struts, that are thicker at their base than their free margin (tear-drop shaped), project from the sewing ring at an angle of less than 90 degrees to form an open cage. Three tiny metal feet project into the valve orifice from the inner ring on the surface opposite the cage ; two act as hinges and the third functions as a disc stopper. The disc is free to distribute wear by moving around, and it is held in place within the housing by its own diameter during ventricular systole. The two long struts prevent the disc escaping through the outflow orifice. When closed the disc just barely overlaps the seat(18).

The valve has given good early results(18), but cardiac catheterization has revealed no superior function of this prosthesis compared to several other types of valve prostheses. Catastrophic thrombosis was a common complication(108-110).

(v) LILLEHEI-MEDICAL VALVE.

This valve was introduced by Lillehei et al.(111) in order to overcome the problems with the Lillehei-Kaster prosthesis. The titanium components which characterized the latter were

replaced by pyrolytic carbon layered over a graphite substrate. The base of the valve was made thinner to incorporate the advantage of the Bjork-Shiley valve regarding the inner-to-outer diameter ratio. The disc was also thinner than before. The design abolished struts and the cage was much shorter.

(vi) HAMMERSMITH VALVE.

The Hammersmith low-profile prosthetic valve(112-114) was introduced in 1964 by Melrose and his colleagues(112). The valve had evolved from from an earlier design of a self-retaining ball-valve(113). The Hammersmith mitral valve was designed to open so that most of the blood flow was directed to the area next to the left ventricular septum below the aortic outflow tract. This meant creating a mechanism similar in action to a hinged flap, but without the disadvantages of a hinge-joint. The initial tilting disc valve (J. B. Flege design) had steel retaining-pins loosely secured within a plastic ring for the hinge mechanism. Another arrangement (F. R. Alvarez Diaz design) repositioned the retaining elements. There were no steel pins and the ring was modified. This design was similar to the original ball-valve except that there were only 2, not three legs attached to the disc and 2 stops protruded from the inner aspect of the ring. Three types of Hammersmith mitral valve prosthesis have been manufactured. Each model aimed to improve the hydraulic function and reduce the tendency to thrombosis on the valve.

The Mark I valve, (used in animal experiments), had 3 legs of equal length supporting a large trapdoor. The Mark II valve used clinically had only two legs and a lighter trapdoor, which opened to one side only. Thus, the valve had to be very accurately placed in the heart so that it opened into the left ventricular outflow tract, because one side was completely occluded when the trapdoor was open. The Mark III valve has 3 legs, two long and one short, so that the trapdoor opens all

around its circumference. Positioning of the valve is less critical with this version. An extension of the ring prevents rotation of the disc. The valves were manufactured and sold by Portland Plastics Ltd., Kent, England.

Shaw et al.(115) reported sudden mechanical malfunction of Hammersmith mitral valve prostheses due to wear of the polypropylene material at the site of contact between the short leg of the disc and the valve ring. Such malfunction resulted from detachment of the disc from the ring or sticking of the disc in the open position. These authors concluded that polypropylene has a low resistance to abrasion and it may not be suitable for prostheses, especially if the design predisposes to localized wear.

Polypropylene is a synthetic polymer produced from the hydrocarbon gas propylene which is obtained by "cracking" oils. It was also used in the Model 6310 Starr-Edwards valve(116). Polypropylene can exist in 3 spatial forms(103) and the proportion of these forms helps determine the properties of a particular batch of the polymer. Prolonged high temperatures make the plastic brittle. Thus, not only the design of the valve, but the mode of production of the plastic itself are important in determining the durability of the prosthesis.

(vii) HALL-KASTER (MEDTRONIC-HALL) VALVE.

The primary goals of the Hall-Kaster prosthesis(117) design were to obtain the least possible obstruction to flow in the open position and to increase the size of the small orifice. All projections into the orifice, including the central disc guide strut, are open-ended to prevent thrombogenesis at these sites. The new pivotal disc mechanism was so designed that when open the disc split the total valve orifice into two nearly equal parts. The disc has a composite, two-part movement. There is a large range of movement and in the aortic position, the disc opens to 75 degrees. The disc is

less than 2 mm in thickness, with an aperture at the centre, and it is made of a graphite substrate containing tantalum which makes the disc radio-opaque. It is Pyrolite-coated for maximum wear, polishability, and has electronegativity.The valve housing consists of titanium and includes an annular valve base, a pair of inflow pivots, a single outflow pivot, and an S-shaped disc guide-strut with a disc stop. The disc is fitted to the guide-strut, which controls the movement of the disc throughout its travel. The valve housing with its open-ended structural members is low in profile and contains no welds or introduced bends(118). The sewing ring is made of knitted Teflon. In the closed position, the disc is parallel to the plane of the valve base and rests within the orifice on the two inflow pivots and the disc stop. To open, the disc lifts slightly, then pivots about the curved end of the outflow pivot through an arc of 75 degrees in the aortic model. Soon after its clinical introduction in 1977, two dimensional changes were made. Firstly, the clearance between the edge of the disc and the ring was reduced in order to lower the degree of regurgitation and theoretically reduce the amount of haemolysis(106). Secondly, the diameter of the sewing ring was reduced by 1 mm to allow insertion of a valve with a larger internal orifice in a given annulus.

Semb et al.(119) reported the first in vivo haemodynamic observations with this prosthesis in both acute and chronic experiments following implantation of the valve in the mitral position in dogs. These studies showed a low transvalvular pressure gradient, an effective opening angle of about 70 degrees and good diastolic flow through both the large and small orifices of the prosthesis. Aasen et al.(120) used anticoagulants and antibiotics to develop a long-term canine model for studying the Hall-Kaster valve in the mitral position. A recent study from South Africa(121) reported the occurrence of intermittent aortic regurgitation in 4 of 160 patients with Hall-Kaster aortic prostheses. In all 4 patients mechanical obstruction to free movement of the disc was

excluded. Wide opening of the occluder beyond the axis of blood flow appeared to be responsible for non-closure of the valve during diastole. The aortic incompetence was corrected by re-orientation of the major orifice of the prosthesis. It is disturbing that such incompetence may be impossible to detect prior to closure of the aorta and discontinuation of cardiopulmonary bypass. These authors believe that the major orifice should face the anterior commissure i.e., between the left and right aortic cusps.

(viii) OMNISCIENCE VALVE.

This valve has four tiny metal struts with angled ends which project into the valve orifice(11). Closure of the orifice is achieved by a thin, curvilinear black pyrolytic carbon-coated disc which pivots between the metal struts. The struts on the inflow surface also angle upwards from the metal inner ring. The disc lies at an angle of 12 degrees when the prosthesis is closed. The sewing ring has 4 black marks on it to help the surgeon to orientate the valve. Despite a short follow-up period, Rabago et al.(121a) noted a significant incidence of valvular dysfunction, which led them to discontinue using the Omniscience prosthetic valve.

(ix) OMNICARBON VALVE.

This prosthesis is similar to the Omniscience valve described above. The difference is that all portions of the valve, including the sewing ring, are covered with black pyrolytic carbon. The dark-coloured sewing ring has 2 or 3 white marks on it for assisting with the orientation of the valve at the time of implantation(11).

(x) SORIN VALVE has been used in Italy. I have been unable to obtain information regarding its structure, but prosthetic thrombosis has been reported(121b).

5. BILEAFLET HEART VALVE PROSTHESES.

(i) KALKE-LILLEHEI DOUBLE LEAFLET VALVE.

The first rigid,bi-leaflet prostheses were described by Kalke and Lillehei in the mid-1960s(122,123). This new design concept was well tested at that time in the pulse duplicator, by animal implantation studies and by cineradiography. The valve had excellent flow characteristics and haemodynamics were better than existing designs. The leaflets and housing were made of titanium and the sewing ring of Teflon. The leaflets opened to an angle of 60 degrees, permitting flow through both the central and lateral areas of the orifice. Each leaflet had two ball-like knobs laterally that pivoted within ovoid recesses in the titanium housing. Thus, while opening the leaflets slid laterally to increase the central orifice as they rotated. During closure the leaflets again moved to meet in the midline leaving only a narrow linear gap. This prosthetic design was further refined and the valve was made totally of pyrolytic carbon. The prosthesis, now called the St.Jude Medical Valve, was ready for in vitro and animal testing in 1976(124).

(ii) St JUDE MEDICAL VALVE.

At the time of writing, this is the newest, 'state of the art' mechanical prosthesis. It is a low profile, lightweight, bi-leaflet, central-flow device made entirely of pyrolytic carbon. It has two semi-circular (D-shaped) discs(125) that open to an angle of 85 degrees from a closed position in which the leaflets lie at 30-35 degrees to the valve housing. An ingenious pivot mechanism eliminates the need for any supporting struts. The two housings containing the pivoting ends of the discs protrude as smooth elevations on the inflow aspect of the valve(11). All portions of the valve (except the

sewing ring) are covered with black pyrolytic carbon. The occluders lie at an angle to each other in the closed position. Controlled leakage aims to minimize thrombosis. There is a seamless, double velour Dacron sewing cuff. A pressure of only 0.8 mm Hg is needed to open or close the valve. The valve design allows for a high ratio of flow orifice to tissue annulus diameter.

Before clinical use of the valve was instituted, an intensive programme of in vitro and in vivo evaluation was performed. The in vitro tests(126) showed the St Jude Medical valve to be safe and effective with superior haemodynamic parameters compared to other clinically available cardiac valvular prostheses. In vivo testing of the valve in calves(127) showed equally promising results. The St Jude Medical cardiac valve prosthesis is presently undergoing extensive world-wide clinical trials. Early postoperative catheterization studies at several centres showed excellent hydraulic function(128).

B. TISSUE VALVES (BIOPROSTHESES).

1. HOMOGRAFT (ALLOGRAFT) AORTIC VALVE.

The varied methods for tissue valve preparation have resulted in some confusion,particularly over exact definitions of valves,which have not been chemically treated(129). This is not surprising, since homograft valves are a variable entity(18) according to (i) the method and timing of collection, (ii) sterilization, (iii) methods of valve storage, (iv) technique of implantation, and (v) use of a free graft or one on a supporting stent. Pioneering work in introducing the clinical use of the viable aortic valve homograft was performed by Carrel(130,131), Gross(132,133), Lam(134), Murray(135), Duran and Gunning(136), Ross(137), and

Barrat-Boyes(138). It was the latter two authors who were the first to (independently from each other) successfully perform orthotopic implantation of a homograft aortic valve. The work of Heimbecker et al.(139) also helped to verify the long-term durability of aortic valve homografts.

(i) FRESH HOMOGRAFT AORTIC VALVE.

Fresh valve is a relative term, not specifying the time period from time of death to procurement(129). Such valves are usually obtained between 4 and 48 hours after death, commonly from males aged between 18 to 40 years. Patients dying with septicaemia (or hepatitis, tuberculosis, or syphilis) are excluded as donors. The adjective viable indicates that the cuspidal fibroblasts are kept alive in vitro and will theoretically be capable of replication and formation of collagen following implantation of the valve in a recipient. Fresh homograft aortic valves implanted in the sub-coronary position proved virtually free of thromboembolic complications without anticoagulant therapy(140). The fresh homograft valves were mounted on a stent to allow such valves to be implanted in other intra-cardiac (e.g., atrio-ventricular) positions(141) and to aid insertion of the graft in the aortic position(125). Angell et al.(142) first used a frame-mounted aortic homograft in 1967.

(ii) STERILIZED HOMOGRAFT AORTIC VALVE.

At first, the valves were removed from cadavers using sterile precautions, but later because of logistical difficulties the method was changed to clean conditions. It thus became important to have a means of ensuring the sterility of the excised valve.

Initially, severe methods(144) were used to sterilize the homograft aortic valves e.g., exposure to ethylene oxide or beta-propiolactone sterilization, irradiation, freezing and

freeze-drying. Such treatment abolished valve viability.A method of sterilization and storage was sought which would maintain valve viability. Surface sterilization using formaldehyde vapour proved to be unsatisfactory(145). The use of in vitro antibiotics in high concentrations(146,147) led to successful sterility, but also yielded a non-viable valve. In order to overcome this problem Angell et al.(143) used non-sterile procurement of the valve homograft and euthermic (37 degrees Centrigrade) incubation of the valves in tissue culture solutions containing physiological doses of selected antibiotics. After trying various combinations of antibiotics, these authors were able to achieve satisfactory sterilization with only a 15% reduction in cuspidal viability. Fungi were not affected by such treatment. Bakst et al.(148) reported good early haemodynamic results with antibiotic-treated homograft aortic valves.

However, there are those who believe that donor cells do not survive after allotransplantation(149). Experimental evidence for continued donor cell survival in valves following allotransplantation is conflicting. Some reports have shown continued donor cell survival in fresh allograft leaflets implanted into dogs(147,150,151), whereas others have reported rapid depletion of cuspidal cellularity after implantation(152-154).

The problem of ensuring viability is compounded by the need for having a means of storing aortic valve homografts of different sizes for more than just a few days. A variety of storage processes have been tried(18,143) including hypothermic storage in tissue culture medium, glycerol or dimethylsulphoxide. Freeze-drying and storage at room temperature was widely used from 1962 to 1968, but there was a high failure rate with such prostheses, since they were effectively composed of dead, acellular, easily degradable tissue.

Homograft valves were not widely used due to the difficulties described above. This was fortunate, since those

subjected to the rigorous sterilization and storage techniques in use up to 1968 had a high failure rate(18). Antibiotic sterilization has been applied more recently and about 50% of such patients have normal valve function 5 years after implantation(18). However, the advantages to the patient with regard to freedom from embolism, anticoagulation, noise and haemolysis justify the use of aortic valve homografts. Due to logistical difficulties, these valves have not been formally utilized at Groote Schuur Hospital.

As noted earlier, in order to use the aortic valve homograft in the mitral position, the valve has to be mounted on a supporting stent to maintain normal cuspidal relationships. The rigid stent leads to greater stresses on the valve with resultant accelerated leaflet degeneration(142). Others are hoping that the use of a pliable stent will reduce the magnitude of this problem(155). Pulmonary valve homografts implanted in the mitral position have been most unsuccessful(156,157). Several reports describe the pathology of the human aortic valve homograft(158-161). Hudson(158) noted thickening of the bases of the cusps of aortic valve homografts in addition to the usual complications that may follow cardiac surgery. Smith(159) noted that calcification occurs as a late complication in the dead tissue of the homograft. Davies et 1.(160) noted "degenerative" changes in the cuspidal collagen of their homografts implanted in patients, as well as calcification and/or rupture or perforation of the cusps. Aparicio et al.(161) studied the microscopical changes in valvular homografts and pig aortic xenografts sterilized by various methods. The freeze-dried valves showed structural changes due to physico-chemical degradation of the collagen due to improper preservation of the graft prior to insertion. Calcification was observed in this group, but not in homografts treated with gamma-radiation. The latter valves showed fewer and less severe morphological alterations.

2. XENOGRAFT AORTIC VALVES.

(i) UNFIXED XENOGRAFT VALVES.

In 1965, Duran and Gunning(162) reported on the behaviour of freeze-dried pig aortic valves transplanted into the descending thoracic aorta of 17 dogs. Although no animal survived for more than 18 months, the xenograft cusps were all in good condition. Duran and Gunning (unpublished data) transplanted a xenograft aortic valve in a very ill patient in 1964. This patient, cited by Binet et al.(163), died 24 hours later from causes unrelated to the xenograft. At necropsy the valve was competent and in good condition. Encouraged by this work, Binet et al.(163) treated xenograft aortic valves by three days immersion in a mercurial solution prior to implanting them into 5 patients. Four patients received pig aortic valves and one was given a calf aortic valve. All 5 patients were doing well at the time of documentation less than 3 months later.

A year later Halseth et al.(164) reported that fresh, sheep aortic valves stored in a lactate-Ringer antibiotic solution had been implanted into the descending aorta of 35 dogs. Only 6 animals survived longer than 7 weeks. Problems encountered included graft thrombosis, cuspidal atrophy and fibrosis. Duran et al.(165) found that ficin-digested and fresh, untreated pig valves gave poor results when transplanted into the canine descending aorta. Freeze-dried valves were associated with a lower operative mortality and an improved mean survival time, but there was a marked tendency for the grafts to rupture through the heterologous aortic wall cuff. Sweatt et al.(166) transplanted aortic aortic valves of sheep and pigs into the descending thoracic aorta of dogs. The valves were fresh, freeze-dried, or treated with propiolactone. Half of the recipient dogs received azathioprine. The following conditions gave the best results : (a) transplantation of a minimum of aortic wall with the valve

; (b) good initial alignment and movement of the cusps ; (c) administration of azathioprine for 8 weeks ; and (d) support of the graft by a Dacron tube, preventing rupture and separating the graft from ingrowing host tissue. Drury et al.(167) compared porcine aortic valves stored in various concentrations of sucrose (50-80%) for up to one year with others stored in a nutrient and antibiotic medium for 12 weeks. They concluded that sucrose solution is acceptable for the long-term preservation of biological valves.

(ii) FORMALDEHYDE-PRESERVED XENOGRAFT.

Obtaining aortic valve grafts from animals overcomes the logistical problems encountered with procuring cadaveric human aortic valves. While fresh valves could be implanted, there is the potential problem of rejection. Also, since the viability of fresh allograft aortic valves was often questionable, attention began to shift from the viability of the cuspidal cells to factors affecting the connective (mainly collagenous) tissue which constitutes the valve substance. Various means of pre-treating the xenograft valve in order to render it less antigenic were evaluated e.g., mercurial salts(168) or 4% buffered formaldehyde solution(169). In 1968, Warren Hancock, an engineer with Hancock Laboratories, Anaheim, California and William Angell of Cutter Laboratories, Berkeley, California, produced the first commercially available prepared tissue valve. This was a formalin-tanned, stent-mounted porcine xenograft. Long-term follow-up in such patients was disappointing. As we shall see later (Chapter 9) the locally prepared University of Cape Town formalin-treated porcine xenografts yielded similar results. Formalin-fixation by cross-linking of valve collagen was found to be reversed in vivo, resulting in stretching, thinning and tearing of the leaflets when the cusp degenerated(143,170).

(iii) GLUTARALDEHYDE-TREATED PORCINE XENOGRAFT AORTIC VALVES.

(a) CARPENTIER PROSTHESIS.

Alain Carpentier(171) showed that the durability of a preserved tissue valve depended upon its own structural integrity. The underlying concept of the porcine aortic valve was changed from that of a graft to that of a bioprosthesis i.e., the tissues used to construct the valves are pre-treated in such a way that they become non-antigenic and stable like a synthetic material. Thus, in contrast to a graft, the durability of the bioprosthesis depends upon the unfailing stability of the biological material and not upon regeneration by host cells. He used sodium metaperiodate oxidation of mucopolysaccharides and glycoproteins to reduce antigenicity and glutaraldehyde to prevent collagen denaturation. The new glutaraldehyde-treated porcine aortic valve was first implanted by Carpentier in 1968 using an asymmetrical stent to support the muscular component of the right coronary cusp(172). Unfortunately, Carpentier's first glutaraldehyde xenograft implants were hampered by poor leaflet mobility and tissue fatigue due to the oxidation step in the tanning process(173).

(b) HANCOCK GLUTARALDEHYDE-PRESERVED PORCINE XENOGRAFT VALVE.

Although formaldehyde is unsuitable for treatment of biological valves because it weakens the chemical cross-linkage bonds in collagen, glutaraldehyde enhances formation of collagen covalent cross-linkage bonds and increases tissue strength(125). Following the promising results obtained by Carpentier's glutaraldehyde treated xenograft valve, Reis and Hancock(174), working at the United States National Institutes of Health and Hancock Laboratories, and Angell first with Cutter and then with Shiley Laboratories

in California, changed from formaldehyde to glutaraldehyde fixation(175). These valves were first used clinically in 1969 and 1970 respectively. There are 3 commercially available glutaraldehyde-treated xenograft valves : from Hancock, Edwards (Santa Ana,California) and Shiley Laboratories.

While these three companies manufacture the porcine bioprosthesis in a very similar manner, specific techniques of tissue handling and valve mounting probably accounts for the main differences between these valve types(163). In the case of the Hancock glutaraldehyde xenograft valve, the stent has a symmetrical and uniform design and the stent material consists of Stellite and polypropylene. The stent itself is covered with Dacron. A 0.2% glutaraldehyde solution is used for pressure fixation of the valve in the closed position prior to suturing of the valve (by continuous and interrupted sutures) to the cloth-covered, semi-flexible stent and for subsequent storage of the manufactured bioprosthesis. A silicone rubber (Silastic) insert within the Dacron cloth ring acts as a cushion to facilitate coaption of the bioprosthesis to the patient's valvular annulus. The prosthesis is radiolucent apart from the metallic ring in the base. The aortic prosthesis (Model 242) and the atrioventricular valve (Model 342) differ only in the shape of their sewing margins. Due to the obstructive effect within the stent of the muscular component to the porcine right coronary cusp, Hancock Laboratories produced a valve (Model 250) in which this cusp was replaced by a non-muscular cusp. This yielded a composite prosthesis with a larger flow orifice.

(c) CARPENTIER-EDWARDS GLUTARALDEHYDE-TREATED PORCINE XENOGRAFT AORTIC VALVE.

The first series of xenograft valves produced by Edwards Laboratories incorporated an oxidation step with sodium metaperiodate before glutaraldehyde fixation(173). This step was abandoned in the mid-1970s(176). The second series of

valves was treated with glutaraldehyde alone. The first such valve was implanted by Dr Carpentier in March 1975 ; the commercially available prosthesis, named the Carpentier-Edwards valve, was generally available from 1976.

The Carpentier-Edwards valve(18,163) is treated in a stronger glutaraldehyde solution (0.625% glutaraldehyde in phosphate buffered saline, pH 7.4) than is the Hancock valve. The compliant metal stent consists of Elgiloy (an alloy of cobalt and nickel made by the Elgiloy Corporation). The entire stent (i.e.,the supporting posts and base frame) is flexible. The inflow orifice is contoured to support the partly muscular, porcine right coronary cusp. The commissural supports are not equidistant and slant inwards at an angle to conform with the anatomical configuration of the porcine aortic valve. The asymmetry allows the use of a larger pig valve for a given stent diameter. The strength and flexibility of Elgiloy allows the use of a thinner metal frame,resulting in an improved orifice-to-annulus ratio(18) of 0.91 (compared to 0.76 for the Hancock valve).

The metal frame is covered with porous, knitted Teflon cloth to facilitate tissue invasion and encapsulation. The sewing ring has a Silastic (silicone sponge rubber) insert, which is covered by a porous, seamless Teflon cloth. As in the Hancock valve, the compliant sewing ring allows coaption between the valve and an often irregular or calcified tissue bed. The pig valve is attached to the stent by both interrupted and continuous sutures.

The current Model 2625 Aortic and Model 6625 Mitral Carpentier-Edwards Bioprostheses have been used clinically since March 1975 in at least seven institutions world-wide. A data sheet issued by Edwards Laboratories in November 1968(177) reported that 0.625% glutaraldehyde is an effective sterilizing agent against a wide variety of organisms including E.coli, Staph. aureus, Streptococcus pyogenes, Candida albicans and 5 species of mycobacteria. Only the mature spore of Chaetomium globosum was found to be resistant

to 0.625% glutaraldehyde. Glutaraldehyde in concentrations up to 10% proved to be ineffective against this organism's mature spore. Formaldehyde in a 4% concentration was found to be an effective sterilizant against this spore. Since studies showed that glutaraldehyde-induced leaflet tissue cross-linkage was not reversed after short-term exposure to 4% formaldehyde, this step was added to the valve preparation as an additional sterilization precaution. The recent Carpentier-Edwards valves are thus treated with both glutaraldehyde and formaldehyde.

As noted earlier, the Carpentier-Edwards valve uses an asymmetric design for the base of the valve to give a more contoured inlet orifice. This design plus the thinner sewing ring provides better hydraulic function than the standard Hancock valve. However, the transvalvular gradients,especially in the small sizes, are still higher than those of mechanical valves. In 1981, Bonchek(125) reported that Edwards Laboratories were introducing a modified xenograft prosthesis with improved hydraulic performance in vitro due to further thinning of both the cloth and metal components of the frame.

(d) ANGELL-SHILEY VALVE.

Dr William W.Angell and his co-workers started making glutaraldehyde-treated porcine aortic valve xenografts in 1970, using the metal stent used earlier in aortic homografts. In 1975, an association was entered into with Shiley Laboratories, and the Angell-Shiley xenograft valve was marketed(18). These valves were treated with 0.5% glutaraldehyde and the flexible stent was made of Delrin and totally covered by Dacron cloth. The stent has an anatomic design derived from castings which were made from the most frequently occurring porcine aortic valve configurations(175). Each pig valve is matched to one of 70 different anatomic stent configurations, which vary in both shape and size. This provides a natural position and support for the valve. The resulting annular sewing rim is not circular in shape and thus

the orificial area of the bare stent is a calculated quantity.

(e) LOW PROFILE BIOPROSTHESIS.

This low-profile, glutaraldehyde-fixed porcine aortic valve is produced by Cientifica Argentina, Buenos Aires, Argentina. Navia et al.(178) report on the hydraulic and haemodynamic features of this valve in 316 patients.

3. AUTOLOGOUS FASCIA LATA VALVE.

Professor Ake Senning(179) of Switzerland in 1962 first implanted an unstented aortic valve prosthesis fabricated from fascia lata. While the patient was on cardiopulmonary bypass, a strip of fascia was taken from the patient's thigh, cleaned and tailored to size. The strip was sutured into the aortic root using continuous sutures and the commissures were attached to the aortic wall by separate,Teflon-felt anchored sutures. Senning's favourable experience with such a valve stimulated Mr.Donald N.Ross and Mr.M.I.Ionescu of Britain to produce a series of fascia lata valvular prostheses for use in the aortic, mitral, tricuspid, and pulmonary positions. In their valves the fascia was mounted on a cloth-covered metal stent. The early results showed a low rate of thromboembolism(180,181).

This encouraged many surgeons world-wide to implant home-made autologous fascia lata valves. Experimental data(182,183) soon began to sound a cautionary note regarding the durability and lack of thrombogenicity of the fascia lata valve. Such valves gave disastrous results when used in the mitral and tricuspid positions(184-187) due to severe regurgitation. Within 3 years after implantation, 90% of mitral valves and 20% of aortic valves had failed(18). Removed valves often showed leaflet shrinkage, retraction and loss of mobility due to overgrowth by host tissue(188,189). A wide

literature documents the meteoric rise and fall in popularity of the fascia lata heart valve(190-234).

4. DURA MATER HOMOGRAFT VALVE.

Dura mater has been used previously to repair inguinal hernias(235) and experimentally to reconstruct the right ventricular outflow tract(236). The external aspect of the dura mater has a smooth, shiny surface and the internal aspect is covered by a layer of arachnoidal endothelial cells(237). At the easily detachable (temporal) area the dura mater is less vascular and it is of uniform thickness,resistance and flexibility. Since the dural double collagen layer has the collagen bundles arranged at right angles to each other, it should be stronger structurally than fascia lata in which there is only a single layer of parallely arranged collagen fibres. The failure of the fascia lata valve led to attempts to fashion a valve from dura mater. This form of prosthesis was pioneered by Professor E. J. Zerbini and colleagues in Brazil(237-239) starting in 1971.

Dura mater was obtained within 20 hours after traumatic death from human cadavers aged between 10-50 years. Cases of infective or degenerative diseases, as well as neoplasia were excluded. The dura mater was removed at autopsy using sterile gloves and instruments. Thereafter it was washed for 1-2 hours in flowing water and then placed in a sterile container filled with 98% glycerol at room temperature for 10-20 days. At the end of this time a sample of the dura was cultured bacteriologically. Zerbini and Puig found that 18.7% of such samples were contaminated and the dura had to be discarded(237).

Before valve construction, the tissue is rehydrated in sterile physiological saline and the valves are then fashioned under operating theatre conditions. The leaflets are separately cut from the dura selecting areas with a similar

texture, thickness and vascularity. The separate cusps are mounted on a Dacron velour-covered, rigid, stainless steel stent and attached to each other by interrupted sutures augmented by Teflon strips. The dura mater is mounted on the outside of the struts, resulting in retention of the full central orifice. Completed prostheses are stored at 4 degrees Centigrade in an antibiotic solution(18). The radio-opaque stent is readily recognizable on x-ray.

The dura mater valve has a low incidence of thromboembolism without anticoagulation(18). Procurement of dura mater is a problem outside large metropolitan areas where trauma victims are less plentiful. Sterility is another important problem, since the efficacy of glycerol in this regard is dubious. The valve has shown a moderately high rate of early and late re-operation. The more recent history of the development and clinical usage of the dura mater valvular bioprosthesis is reflected in references 240-249. This prosthesis is no longer used.

5. BOVINE PERICARDIAL XENOGRAFT BIOPROSTHESES.

(i) IONESCU-SHILEY VALVE.

In 1970 Dr Marian I.Ionescu began constructing and testing glutaraldehyde stabilized pericardial xenografts(250,251). Between March 1971 and April 1976 the valves were constructed in limited numbers in his own laboratory in Leeds, England and used for single valve replacements only(252). Following on the good results obtained after 5 years of clinical testing(253), from May 1976 the Ionescu-Shiley pericardial xenograft valve became available from Shiley Laboratories Inc., Irvine, California, U.S.A.

The Ionescu-Shiley valve(18,252,254) consists of bovine pericardium mounted on a Dacron cloth-covered pure titanium support stent. The sewing ring consists of porous Dacron

fabric covered with a thin layer of Dacron cloth. All valve sizes have the same sewing ring configuration and there is no difference between valves used in the aortic or atrioventricular positions, either sub- or supra-annularly.

The pericardium is obtained from 6-18 months old calves which have been certified as being fit for human consumption by the United States Food and Drug Administration. Sterile procedures are used from the time the pericardium is harvested. The pericardium is first placed in a balanced electrolyte solution to remove soluble antigenic proteins. Thereafter it is stored at 4 degrees Centrigrade for 2 weeks in 0.5% glutaraldehyde buffered to pH 7.4 with 0.067 M phosphate(240). This treatment aims to reduce or eliminate antigenicity and prevent collagen denaturation by forming irreversible covalent cross-links between the amino groups of collagen and glutaraldehyde(18). A single strip of pericardium is used per prosthesis and the tissue is stitched to the outside of the stent to maintain an excellent orifice-to-annulus diameter ratio. For example : the orifice-to-annulus ratios for various 23 mm prostheses are 0.65 for the Starr-Edwards caged-ball valve, 0.70 for the Lillehei-Kaster pivoting disc valve, 0.78 for the Bjork-Shiley tilting disc valve and 0.84 for the Ionescu-Shiley valve(18). Such an advantage is important in small aortic sizes. The strut posts of small valves (17 to 23 mm annulus diameter) are splayed 9 degrees outward to maintain the full central orifice.

The valves manufactured in Ionescu's own laboratory between 1971 and 1976 underwent little, if any, quality control(252) and no standardization of thickness and pliability of the cusps was attempted. Also these early valves were pre-treated with sodium metaperiodate and ethylene glycol prior to fixation in a simple dilution of commercially available, non-purified glutaraldehyde. The latter has an unknown and unstable proportion of monomers and polymers(251). Aqueous solutions of glutaraldehyde are complex mixtures of

free glutaraldehyde, mono- and dihydrate glutaraldehyde, cyclic monomer and polymer glutaraldehyde and alpha, beta unsaturated glutaraldehyde polymers. The importance of glutaraldehyde polymerization has not been well understood. It would appear that monomeric glutaraldehyde is not an effective fixative because a longer chain polymer is necessary in order to bridge the gap between the collagen protein amino acid molecules(175). Solutions containing high concentrations of very long-chain glutaraldehyde polymers are poor fixatives due to the reduced number of active aldehyde groups available for cross-linking. Pure solutions of relatively short-chain polymers appear to provide optimal fixation(252,253).

Since 1976 the pericardial xenografts produced by Shiley Laboratories have been treated with a solution of 'purified glutaraldehyde' containing the optimal proportion of monomers and polymers and an ideal cross-link density achieved by controlling the concentration and pH of the solution as well as its temperature and the exposure time. The completed bioprosthesis is transported and stored in 4% buffered formaldehyde to maintain sterility.

Ionescu's data(250-252) showed that the pericardial valve had a low thrombogenicity without anticoagulants, an absence of catastrophic failure, good haemodynamic function and lack of haemolysis (if no paravalvular leak was present). However, the narrow unpadded sewing ring appeared to predispose to a high incidence of perivalvular leakage after aortic valve replacement(18,252). While the valve appears to give good service in the aortic position, the 3 year re-operation rate of nearly 12% after mitral valve replacement and the established poor durability record of other tissue valves(18) in this position leaves a question mark over this prosthesis for mitral valve replacement. Pathologic data on a few Ionescu-Shiley valves encountered in hearts received for examination from another hospital (see Chapter 13) as well as in experimental implants performed in baboons (Papio ursinus) in our institution (see Chapter 16) are recorded later in this

study. Published experience(254-267) with follow-up periods of up to 10 years(261) records a low incidence of valve-related complications. Calcification of the prosthesis militates against its use in children(265).

(ii) EDWARDS PERICARDIAL VALVE.

The bovine pericardial valve produced by Edwards Laboratories differs from the Ionescu-Shiley valve in the following respects : (a) The frame is totally made of flexible Elgiloy wire rather than rigid titanium. Thus, both the orifice and the supports are flexible. (b) The pericardium is treated with 0.625% glutaraldehyde rather than a 0.5% concentration. (c) There are different sewing ring arrangements for the aortic and atrioventricular prostheses. (d) The valve is transported and stored in glutaraldehyde rather than formaldehyde.

(iii) MITROFLOW BOVINE PERICARDIAL HEART VALVE.

In 1982 Professor C.N.Barnard and his colleagues at Groote Schuur Hospital and the University of Cape Town, South Africa implanted in baboons (Papio ursinus) a series of bovine pericardial heart valve prostheses constructed by Mitral Medical International Inc., of Wheat Ridge, Colorado, U.S.A. These valves have been made from glutaraldehyde-treated bovine pericardium. The valves have also been evaluated in a canine model in the United States of America. These results have not yet been published in any medical journal (see Chapter 16). The valves have been implanted in a large number of patients in Spain and in less than a dozen patients at Groote Schuur Hospital.

(iv) MEDOX UNICUSPID BOVINE PERICARDIAL HEART VALVE.

In a lecture to the Southern Africa Cardiac society on

March 7,1984 Professor R. W. M. Frater mentioned that the Albert Einstein College of Medicine would shortly be marketing a unicuspid pericardial heart valve. The single cusp is the only moving component of the valve and it closes against an immobile pericardial baffle.

6. ABIOMED POLYMERIC PROSTHESIS.

The Abiomed polymeric trileaflet heart valve prosthesis was originally designed for use in valved conduits. Flow studies indicate that overall it has improved leaflet motion and pressure drop characteristics compared to the Carpentier-Edwards porcine and Ionescu-Shiley pericardial tissue valves in current clinical use. The Abiomed valve is, however, more stenotic than the St Jude Medical and Medtronic-Hall low-profile valves at normal cardiac outputs(268).

C. VALVE-CONTAINING CONDUITS.

1. PULMONARY ARTERY AND VALVE SUBSTITUTES.

Tubular conduits containing valvular prostheses have been used clinically as pulmonary artery and valve substitutes in complex congenital heart disease(18). In patients with transposition of the great arteries undergoing surgical correction, the finding of pulmonary obstruction too severe to be eliminated by excision is an indication for a Rastelli operation(269). In this procedure the left ventricular flow is diverted via an intraventricular conduit through the ventricular septal defect into the aorta. The pulmonary artery is divided and the proximal (cardiac) stump is ligated. An extra-cardiac valved conduit restores continuity between the right ventricle and the distal pulmonary artery.

Kirklin(270) used a composite conduit for repair of pulmonary valve and pulmonary artery atresia associated with a

ventricular septal defect. The conduit consists of an artificial graft containing a homograft valve. The valve is inserted into a sleeve of knitted Dacron secured with 3 sutures proximally and distally. The knitted Dacron graft containing the homograft valve is then interposed between 2 woven Dacron grafts. The distal end of this composite graft is then fashioned according to the pathological features of the pulmonary arteries and is sutured distally. The proximal end of the graft is sutured to an opening in the right ventricle.

Artificial tube grafts containing valvular prostheses have also been used for the correction of other complex congenital cardiac diseases e.g., a persistent truncus arteriosus (common aorticopulmonary trunk)(271).

2. LEFT VENTRICLE-TO-AORTA BYPASS.

Following upon the above described successful use of valved conduits to correct right-sided cardiac defects, attempts have recently been made to apply similar techniques to left-sided cardiac lesions(18). The first fully reported clinical use of the double-outlet left ventricular concept for patients with severe aortic stenosis was that of Bernhard et al.(272). Their patient also had hypoplasia of the aortic ring and of the ascending aorta.

Apico-aortic shunts are primarily used in persons with complex forms of supravalvular or subvalvular aortic stenosis in whom complex surgery in the aortic root may be avoided(18). The conduits may also have a potential role to play in patients with infective endocarditis where the infection has left insufficient tissue in the aortic ring for the suturing of a valve prosthesis.

All of these apico-aortic shunts appear to need to have a rigid outlet connector in order to prevent occlusion of the apical outflow tract by myocardium. The conduits may differ with regard to the type of valve they incorporate and the location of the distal anastomosis. Tissue valves have been

the most popular, because most conduits have been used in children in whom freedom from anticoagulants is an advantage. However, lack of long-term durability may limit the use of such valves. Several firms manufacture conduits :

(a) Thermo Electron Corporation, Waltham, Massachussetts make a rigid U-shaped stainless steel tube, which is coated externally with a layer of polyurethrane(261). The inner aspect is lined with Dacron fibrils and the distal end consists of tubular Dacron which may be connected to a valve-containing Dacron tube graft.

(b) Texas Technology Transfer Laboratories, Inc. make a rigid ventricular tube made of bevelled pyrolytic carbon with a Teflon felt sewing margin and a woven Dacron tube graft is attached distally(273).

(c) Hancock Laboratories initially made a conduit with a Stellite frame covered by polyurethrane(18), but the more recent device uses a semi-rigid polypropylene support and the internal surface is lined with Dacron fabric.

3. REPLACEMENT OF AORTIC VALVE AND ASCENDING AORTA.

As a safer procedure in patients with ascending aortic aneurysms and severe aortic incompetence, Bentall and De Bono(273) used a conduit consisting of a Starr-Edwards valve in a Teflon tube graft to join the aortic valve ring to the distal non-aneurysmal aorta. This technique obviates placing sutures in the often diseased aortic root. The coronary ostia are sutured to holes made in the tube graft. Lefrak and Starr(18) comment that this technique holds promise for patients with very small aortic valve rings who require aortic valve replacement.

CONCEPTS AND ENGINEERING EVALUATION OF HEART VALVE SUBSTITUTES

For additional information regarding biomaterials and

design of valvular prstheses references 266-288 should be consulted. A number of papers deal with the in vitro testing of heart valve prostheses(289-306), whilst others give special consideration to tissue-derived prostheses(307-316). The search for the ideal prosthesis is a continuing one and modern thoughts are again turning towards the concept of a synthetic valve (Mr G.Keith Gielding, Mitral Medical Inc., personal communication). A similar earlier concept, the synthetic Hufnagel trileaflet prosthesis(317) gave poor clinical results.

IDENTIFICATION OF PROSTHETIC HEART VALVES

Several articles outline the morphological(6,9-11) and radiological(318,319) criteria for the identification of prosthetic heart valves. Such identification has been rendered important due to the continuing introduction of new prosthetic heart valves and the increasing awareness of prosthesis-related complications. The operation notes are often not available to the pathologist performing an autopsy on such patients.

Firstly, one has to decide if the valve in question is a mechanical prosthesis (made of artificial materials) or a xenograft prosthesis (made of biological tissue). With regard to the mechanical prostheses, there are high-profile valves which have a ball as the mobile portion (Starr-Edwards, Smeloff-Cutter, DeBakey-Surgitool, Braunwald-Cutter, Magovern-Cromie, Harken, and Surgitool 200 prostheses) and the low-profile valves which have a mobile disc. The latter include the following prostheses : Lillehei-Kaster, Wada-Cutter, Bjork-Shiley, Cooley-Cutter, Kay-Suzuki, Harken, Starr-Edwards model 6520, Cross-Jones, Beall model 103, Beall-Surgitool model 105, and the Kay-Shiley (T series, K series, MGCD series and TGCD series) prostheses.

Next the number of struts should be examined. With the

low profile valves it is important to note whether the struts have an acute angle to the base ring plane (Lillehei-Kaster), emerge into the valve orifice (Wada-Cutter, Bjork-Shiley), or arise at right angles to the base ring plane (Cooley-Cutter, Kay-Suzuki, Starr-Edwards models 6500 and 6520 disc valves, Harken disc valve, Cross-Jones, Beall model 103, Beall-Surgitool model 105, and Kay-Shiley (series T, K, MGCD, TGCD) prostheses.

Note whether the cage is single (Starr-Edwards) or double (Smeloff-Cutter) and whether the cage is open (Braunwald-Cutter, Magovern-Cromie,and Starr-Edwards models 2300, 2310, 6300, 6310). In the latter Starr-Edwards models the cloth covering the struts obscures the opening, which is easily identified only by radiography. The Magovern-Cromie valve has a large cage opening, whereas the above-named Starr-Edwards models have a small cage opening. The other models of the Starr-Edwards prostheses have a closed cage. References numbers 6,9-11,183,184 should be consulted for further details regarding such distinguishing features as the strut-ring junction, the shape of the base ring edge, the site at which the poppet seats (e.g., near its equator or otherwise), radiolucency of the ball or of the disc occluder.

Radiography of the prosthesis at postmortem may help the pathologist identify the type of heart valve prosthesis he is dealing with. This is especially helpful in the case of the currently available xenograft prostheses. Whereas the x-ray of the Hancock porcine aortic valve prosthesis, like that of the Hancock pericardial heart valve, reveals only a narrow wire-like base ring (please see Fig. 12.2 of Chapter 12), the Carpentier-Edwards xenograft valve has a radiolucent base ring and only the serpentine-like wire stent is radiopaque (Fig. 2.4). Mehlman(319) has recently reviewed the radiographic features of ten of the newer valvular prostheses marketed in the United States of America since 1978. This updates an earlier report(318). The base ring and stent of the Hancock II porcine xenograft valve are radiolucent. Three tiny circular

rings mark the distal external aspects of the 3 supporting posts. Although superficially similar to the radiographic silhouette of the Carpentier-Edwards Bioprosthesis, in the Carpentier-Edwards Supra-Annular Bioprosthesis the change of shape of the wireform as it shifts from base ring to stent is more gradual, giving the wire a gently curving instead of a right-angle appearance.

In the Carpentier-Edwards pericardial valve prosthesis the base ring is marked radiographically by a flattened circular ring with three holes. The flattened ring does not extend into the stent as is the case with the Ionescu-Shiley xenograft (Fig. 2.4). In addition, a narrow wireform outlines each of the 3 stent posts and the base ring. In the case of the Ionescu-Shiley xenograft valve the base ring and stent form a single radiopaque structure which appears flattened with many perforations in both. By contrast the Ionescu-Shiley Low Profile Pericardial Xenograft has a base ring consisting of 3 narrow wireform arcs, each length being approximately one-third of the circumference of the base ring. Adjoining arcs are separated by small radiolucent areas. The stent posts are radiolucent.

The St Jude Medical valve, which has 2 leaflets that open to right-angles to the base ring, is radiolucent. When viewed on edge, the discs may be weakly radiopaque. The Bjork-Shiley heart valve prosthesis with the convexo-concave disc has the same x-ray appearance as the Bjork-Shiley valve with the straight disc and incorporated disc marker. Emerging from the base ring towards its centre are 2 eccentrically located U-shaped structures of unequal size. The radiolucent disc contains a narrow, circular radiopaque disc marker. The Bjork-Shiley Integral Monostrut cardiac valve prosthesis has only one U-shaped structure. Perpendicular to the flattened portion of the U is a short straight projection with a very small hook or bulge on its end. The radiolucent disc also has a radiopaque circular disc marker. Due to strut fractures, this prosthesis has been removed from the market.

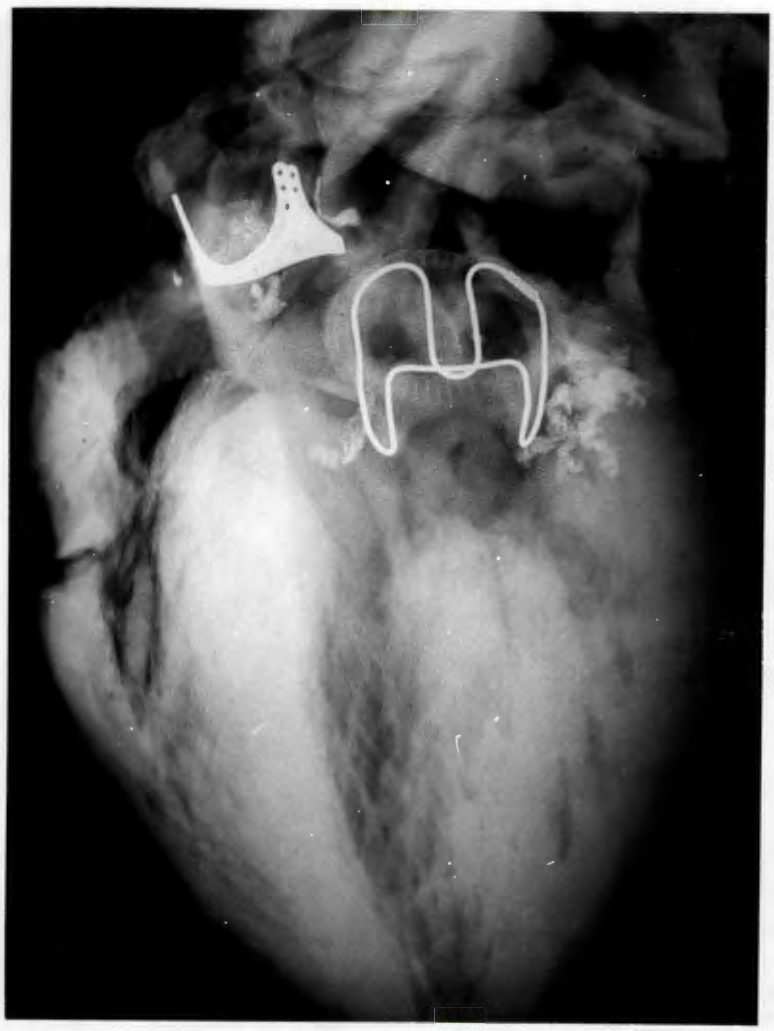


Figure 2.4 : Postmortem radiograph of a heart containing two xenograft bioprostheses. The Ionescu-Shiley aortic valve prosthesis has a solid continuous base ring and stent (with circular perforations), whereas the Carpentier-Edwards porcine aortic valve prosthesis has a radiolucent base ring and a radiopaque, serpentine-like wire stent.

CHAPTER 3.

PATHOLOGY OF NATURAL HEART VALVES AND INDICATIONS FOR HEART VALVE REPLACEMENT

CHAPTER 3.

PATHOLOGY OF NATURAL HEART VALVES AND INDICATIONS FOR HEART VALVE REPLACEMENT

In this chapter I shall pay attention to pathological conditions warranting replacement of heart valves, and discuss the clinical indications for heart valve replacement, the problem of matching prosthesis to patient, and trends in cardiac surgery at the University of Cape Town. One hundred consecutive valve replacement operations will be analysed with regard to the aetiology of the native valvular disease and the incidence of Aschoff bodies in surgically resected atrial appendages.

A. PATHOLOGY OF CARDIAC VALVES WARRANTING REPLACEMENT BY VALVE PROSTHESES.

Before reviewing the clinical indications for heart valve replacement, I would like to examine the various types of valvular diseases which may necessitate heart valve replacement. This survey of valvular pathology covers 18,132 autopsies performed in the University of Cape Town Pathology Department during the 30 year period 1950-1979.

1. ACQUIRED VALVULAR HEART DISEASE IN 1225 AUTOPSY PATIENTS ENCOUNTERED OVER A 30 YEAR PERIOD :

Table 3.1 gives the functional classification of the clinically significant acquired valvular heart diseases encountered in 1225 autopsy patients (6.8%) during this period. Table 3.2 indicates associated involvement of other valves. In Cape Town the mitral valve (Figs. 3.1 and 3.2) is the most commonly diseased heart valve (52.1% of acquired valvular diseases), followed by the aortic valve

TABLE 3.1 : AETIOLOGY OF ACQUIRED VALVULAR HEART DISEASE IN 1,225 NECROPSY PATIENTS

	MS(%)	MI(%)	AS(%)	AI(%)	TVD(%)	PVD(%)
RHEUMATIC FEVER	444(99.8)	133(69.8)	139(46.3)	76(41.8)	8(79.4)	
UNCLASSIFIED		3(1.6)	87(29)*			
AORTIC NODULAR SCL.			64(21.3)			
INFECTION		34((17.6)	10(3.3)	60(33)	18(17.7)	2(66.7)
SYPHILIS				17(9.3)		
MEDIONECROSIS				17(9.3)		
FLOPPY VALVE		13(6.7)**		2(1.1)	2(2)	
RESTRICTIVE CM.		6(3.1)				
RUPTURE PAPILLARY M.		3(1.6)				
RHEUMATOID ARTHRITIS				3(1.6)		
LOST COMM. SUPPORT						
(a)FALLOT-TYPE VSD				2(1.1)		
(b)AORTIC DISSECTION				3(1.6)		
WHIPPLE'S DISEASE	1(0.2)					
ANKYLOSING SPOND.				1(0.6)		
EHLERS-DANLOS SYNDR.				1(0.6)		
CARCINOID SYNDR.					1(1)	1(33.3)
SYSTEMIC LUPUS ERYTH.		1(0.5)				
TOTALS	445 (36.3%)	193 (15.8%)	300 (24.5%)	182 (14.9%)	102 (8.3%)	3 (0.3%)

GRAND TOTAL = 1,225 (6.8% of 18,132 autopsies).

* 81 of the patients had isolated AS ; ** one patient had Marfan's syndrome
CM = cardiomyopathy ; COMM = commissural ; VSD = ventricular septal defect ; M = muscle ; MS = mitral stenosis, MI = mitral incompetence, AS = aortic stenosis, AI = aortic incompetence, TVD = tricuspid valve disease, PVD = pulmonary valve disease ; ERYTH = erythematosus ; SCL = sclerosis ; SPOND = spondylitis ; SYNDR = syndrome.

TABLE 3.2 : COMBINATIONS OF ACQUIRED VALVULAR LESIONS IN 4 DIFFERENT FUNCTIONAL CLASSES OF AUTOPSY PATIENTS WITH HEART DISEASE.

MOST SIGNIFICANT FUNCTIONAL VALVE LESIONS	No. PTS. (%)	ANATOMICAL CLASSIFICATION				
		AV(%)	MV(%)	MV,AV(%)	MV,TV(%)	MV,AV,TV(%)
AORTIC INCOMPETENCE	182(16.3)	102(56)	0	70(38.5)	0	10(5.5)
AORTIC STENOSIS	300(26.8)	145(48.3)	0	139(46.3)	0	16(5.3)
MITRAL STENOSIS	445(39.7)	0	285(64)	111(24.9)	19(4.3)	30(6.7)
MITRAL INCOMPETENCE	193(17.2)	0	104(53.9)	70(36.3)	11(5.7)	8(4.2)
TOTAL	1,120	247 (22.1%)	389 (34.7%)	390 (34.8%)	30 (2.7%)	64 (5.7%)

TABLE 3.3 : RATES OF RHEUMATIC MITRAL STENOSIS (MS) PER 100 AUTOPSIES

	1950-1959	1960-1969	1970-1979
PTS. WITH MS	132	148	124
No. OF AUTOPSIES	5428	4915	4120
RATE/100 AUTOPSIES	2.43	3.01	3.01

Figure 3.1 : Severe rheumatic stenosis of mitral valve orifice due to commissural and chordal fusion. The cusps and chordae are also shortened.

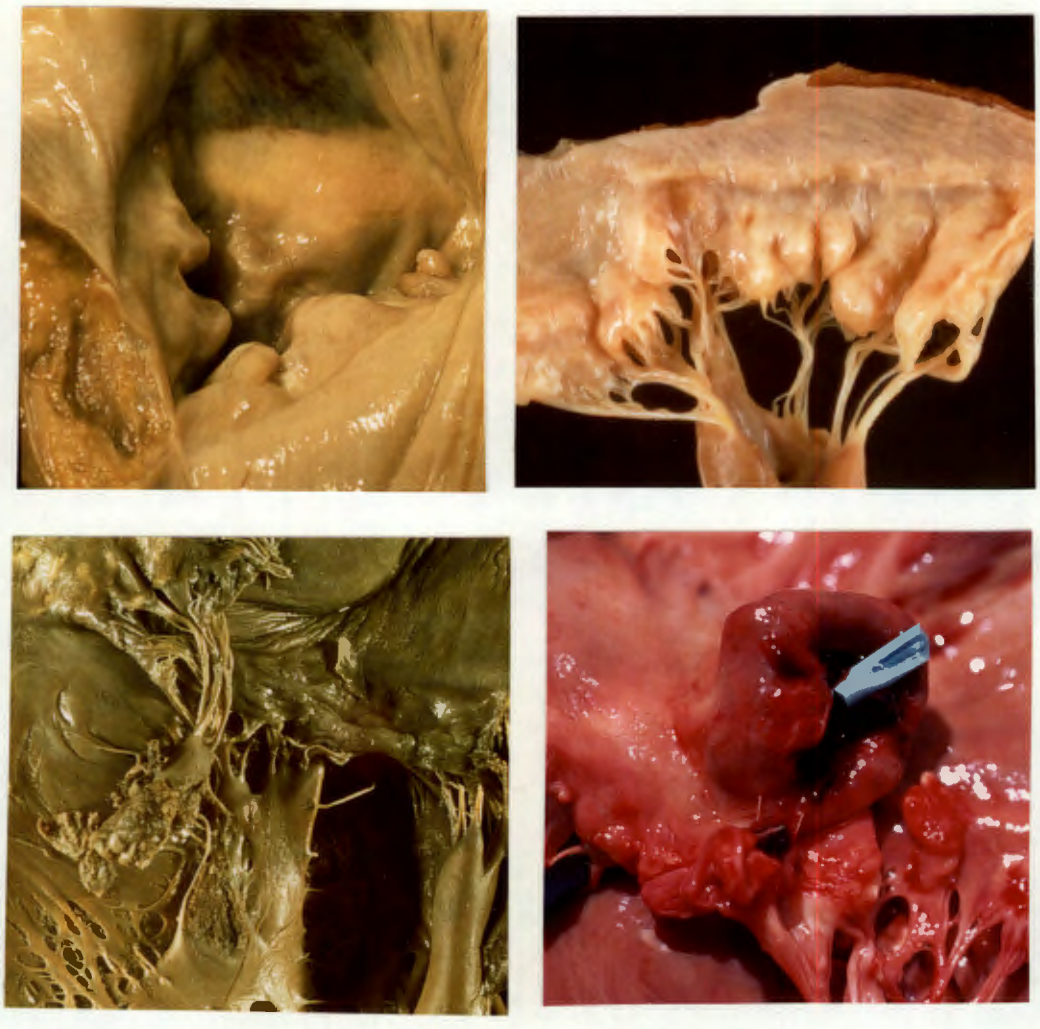


Figure 3.2 (clockwise from top left) : left atrial view of floppy mitral valve ; appearance of opened floppy valve ; ruptured mycotic aneurysm of infected anterior mitral leaflet ; ruptured head of infarcted postero-medial papillary muscle.

TABLE 3.4 : TYPES OF CONGENITAL HEART DISEASE IN 358 AUTOPSY PATIENTS COMPRISING 2.0% OF 18,132 AUTOPSIES ENCOUNTERED OVER THE 30 YEAR PERIOD 1950 - 1979.

MITRAL VALVE		
STENOSIS	5 (1.4%)	
INCOMPETENCE	4 (1.1%)	29
ATRESIA	20 (5.6%)	
AORTIC VALVE		
STENOSIS	7 (2.0%)	
ATRESIA	12 (3.4%)	31
CALCIFIED BICUSPID	12 (3.4%)	
INCOMPETENCE	0	
TRICUSPID VALVE		
STENOSIS	10 (2.3%)	
ATRESIA	12 (3.4%)	30
STRADDLING	3 (0.8%)	
EBSTEIN'S ANOMALY	5 (1.4%)	
INCOMPETENCE	0	
PULMONARY VALVE		
STENOSIS	24 (6.7%)	
FALLOT'S TETRALOGY	82 (22.9%)	146
ATRESIA	40 (11.2%)	
COMMON ATRIOVENTRICULAR CANAL	14 (3.9%)	
SUBAORTIC STENOSIS	9 (2.5%)	
DOUBLE OUTLET RIGHT VENTRICLE	15 (4.2%)	
PERSISTENT TRUNCUS ARTERIOSUS	22 (6.2%)	
COMPLETE TRANSPOSITION	62 (17.3%)	
TOTAL	358	

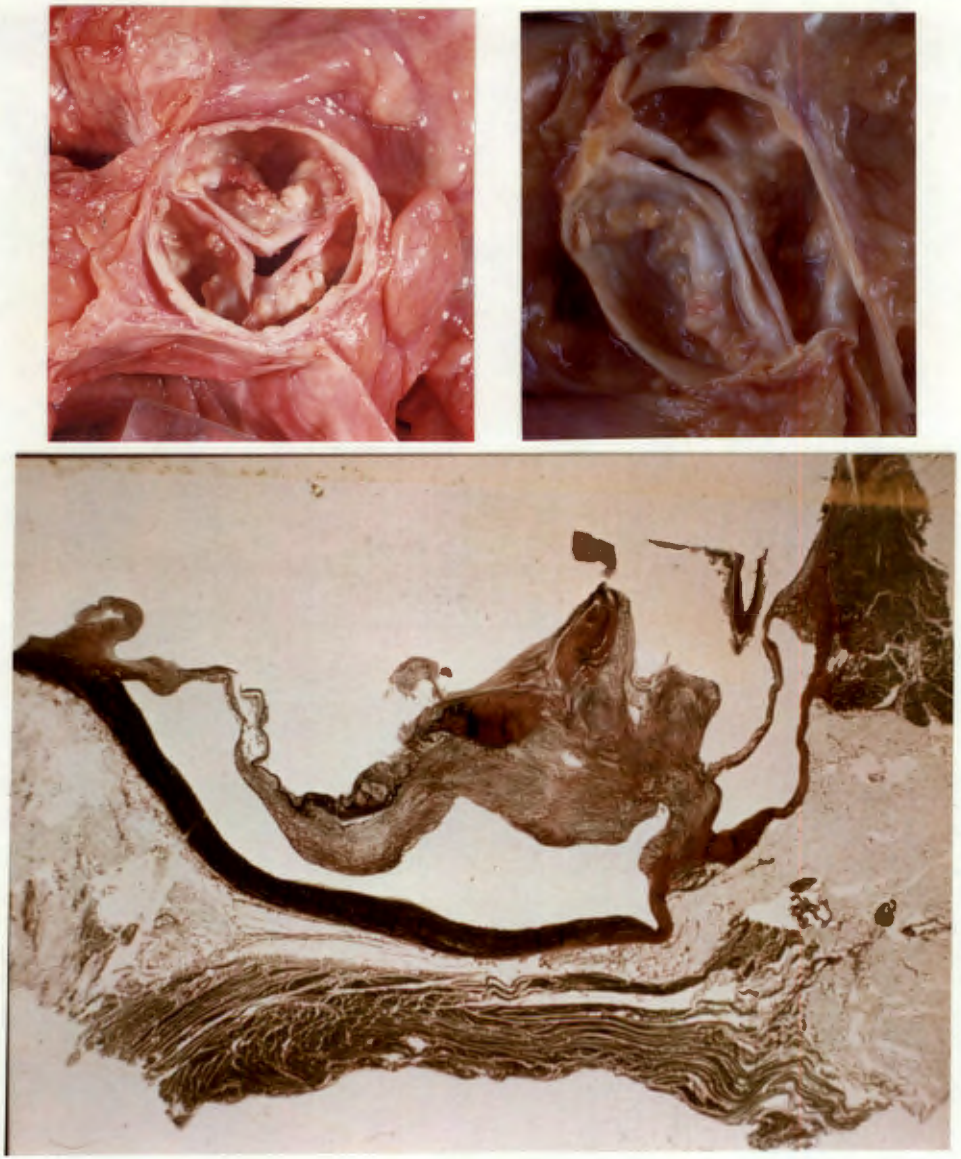


Figure 3.3 : Aortic nodular sclerosis (top left) ; calcified congenital bicuspid aortic valve (top right) ; histology of a transversely sectioned congenital bicuspid aortic valve (below).

(39.4%), and the tricuspid (8.3%) and pulmonary valves (0.3%). In none of our patients was tricuspid valvular disease the most significant functional lesion ; usually it was associated with more severe disease of the mitral and aortic valves. Rheumatic-type valvular disease accounted for 99.8% of the cases of mitral stenosis and 68.9% of patients with mitral incompetence. This overall pattern of descending order of disease involvement of the mitral, aortic, tricuspid and pulmonary valves is similar to that seen in other developing countries e.g., India and in the countries of South America. In the more developed countries of Europe and North America the frequency and severity of rheumatic fever have diminished(1-4). In the United States, Roberts et al.(5) found at necropsy that aortic stenosis was twice as frequent as mitral stenosis. My data show that mitral stenosis, (usually attributed aetiologically to rheumatic fever), is approximately a third more common than aortic stenosis (Table 3.1). Table 3.3 shows that our autopsy incidence of mitral stenosis has not diminished over the 30 year period 1950 to 1979. Thus, Cape Town still has a relatively high autopsy incidence of rheumatic-type heart disease. My findings confirm a recently published analysis(5a) of the incidence of rheumatic fever in children in South Africa and abroad. In the United Kingdom and Japan, the incidence rate of rheumatic fever is 0.06/1,000 inhabitants and in America it is 0.7/1000. A conservative estimate(5a) of the incidence of rheumatic fever in South Africa is 7/1,000 inhabitants and in Natal Indians it is 11/1000.

Whereas rheumatic fever was the apparent cause of virtually all of our cases of mitral stenosis, only 46.3% of acquired aortic stenosis was due to chronic rheumatic-type deformity. In 81 out of the 87 patients (93%) with unclassified aortic stenosis the aortic valve was the only diseased heart valve. According to Roberts et al.(5) such isolated valvular aortic stenosis is nearly always non-rheumatic in origin and most commonly represents a

congenital malformation of this valve(6,7). Davies(8) states that the predominant cause of isolated aortic valve stenosis is premature calcification of a congenitally bicuspid valve. Many pathologists are apt to wrongly diagnose such valves as aortic nodular sclerosis (tricuspid senile calcific stenosis). Indeed, a calcified bicuspid aortic valve was found in our pathology museum wrongly labelled as an example of aortic nodular sclerosis. This diagnostic pitfall is facilitated by the fact that the congenitally bicuspid aortic valve only develops stenosis as cuspidal calcification commences from middle age onwards.

Aortic nodular sclerosis (Fig. 3.3) accounted for less than a quarter of our cases of aortic stenosis. Healed infective endocarditis was regarded as the cause of aortic valve stenosis in 3.3% of patients. Rheumatic fever, infective endocarditis, syphilis (Fig. 3.4) and aortic medionecrosis were the commonest cause of aortic regurgitation (Table 3.1). Tricuspid valve disease (incompetence and/or stenosis) was mainly due to rheumatic-type involvement, with smaller contributions made by infective endocarditis and myxomatous degeneration (floppy valve). The latter two conditions were more commonly noted in the mitral valve. The floppy valve was only recognized as an entity in the mid-1960s. The floppy valve was first diagnosed at autopsy in our Pathology Department in 1973. Thus, our earlier autopsy data do not give its true incidence and this means that our overall incidence figure for floppy valves over the 30 year study period is too low.

Figure 3.4 : Aortic incompetence due to healed syphilitic aortitis (top picture). Bottom picture shows aortic stenosis due to calcification of a congenital, unicuspid, unicommissural aortic valve.

2.CONGENITAL HEART DISEASE IN 358 AUTOPSY PATIENTS WITH EMPHASIS ON CONDITIONS THAT MAY REQUIRE TREATMENT BY VALVE REPLACEMENT OR USE OF A (VALVED) CONDUIT.

Congenital heart diseases, which may require treatment by valve replacement or use of a valved conduit, are indicated in Table 3.4. These data are derived from 358 autopsy patients with congenital cardiac disease who comprised 2% of 18,132 autopsies performed over the 30 year period 1950-1979. Data on diseases not necessarily treated by valve replacement or use of a conduit are included for comparative purposes. Even if cases of Tetralogy are excluded, congenital pulmonary valve disease was twice as common as other congenital valvular disease.

Closed valvotomy in congenital mitral stenosis has not yielded good results, and open operation is advocated(9). Both medical and surgical treatment for mitral atresia give poor results. Congenital mitral incompetence may require mitral valve replacement. Aortic stenosis may be present from birth or it may develop as a result of cuspidal calcification in later life e.g., in a unicommissural aortic valve (Fig. 3.4).

B.CLINICAL INDICATIONS FOR HEART VALVE REPLACEMENT.

Several reports deal with the pathophysiological and clinical aspects of diseases of the natural heart valves(10-18) and others consider the general aspects of heart valve surgery(19-27). There is no clinically applicable test for accurately measuring the functional capacity of the heart. In general, the best index is provided by the classification of the New York Heart Association, which is based on the patient's history of past and present disability and is uninfluenced by the presence or absence of physical signs :

CLASS I. Patients with cardiac disease and no limitation of physical activity. Patients in this class do not have symptoms of cardiac insufficiency, nor do they experience

anginal pain.

CLASS II. Patients with cardiac disease and slight limitation of physical activity. They are comfortable at rest, but if ordinary physical activity is undertaken, discomfort results in the form of excessive fatigue, palpitations, dyspnoea, or anginal pain.

CLASS III. Patients with cardiac disease and marked limitation of physical activity. They are comfortable at rest, but less than ordinary activity causes discomfort in the form of excessive fatigue, palpitations, dyspnoea, or anginal pain.

CLASS IV. Patients with cardiac disease and inability to perform any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may occur even at rest, and if any physical activity is undertaken, discomfort is increased.

1.ACQUIRED VALVULAR HEART DISEASE.

All surgery for acquired valvular disease is palliative only. Working together, the cardiologist and cardiac surgeon must select for operation those patients in whom heart valve replacement (with its attendant operative and long-term risks) offers a better prognosis for health and longevity than continued medical therapy.

MITRAL VALVULAR DISEASE :

Mitral valvotomy is usually performed on patients with severe mitral stenosis and an aggravation of symptoms (in class III of cardiac function by the New York Association Classification.) not due to medically remediable causes. Some patients are only referred for surgery once they are totally disabled (class IV of cardiac function). All closed operations should be performed with the immediate availability of cardiopulmonary bypass, so that valve replacement may be

performed if valvotomy is unsuccessful. If severe cuspidal calcification accompanies the stenosis, then mitral valve replacement is usually indicated(28). Patients with similarly severe disability due to severe mitral regurgitation resulting from a badly damaged valve may also require valve replacement. Fortunately patients with both mitral stenosis and mitral insufficiency run protracted courses even after symptoms develop. Thus the timing of the surgery can be selected deliberately by both the patient and his doctors.

AORTIC VALVULAR DISEASE :

Critical aortic valve stenosis, and mild stenosis associated with severe coronary arterial atherosclerotic narrowing may both give identical symptoms. The first requires aortic valve replacement and the other does not. The clinical and angiographic means of distinguishing between these two conditions is beyond the scope of this review. The combination of severe coronary artery disease and severe aortic stenosis (or incompetence) is usually an indication for surgery in symptomatic patients since the medical prognosis is ominous(28).

Unlike mitral valve disease, patients with aortic valve disease often do well for a long time, but their condition deteriorates rapidly once symptoms appear. Accentuated angina pectoris or angina at rest, syncope (especially on effort), and accelerated dyspnoea or pulmonary oedema indicate a grave prognosis. Such patients are at risk for sudden death. The decision to operate must be made expeditiously soon after the onset of symptoms in these patients.

MULTIVALVULAR DISEASE :

The combination of aortic and mitral disease is usually due to rheumatic fever. Usually bivalvular disease has a long course similar to that of isolated mitral valve disease.

Indications for surgery are similar to those for isolated mitral or aortic valve disease.

TRICUSPID VALVULAR DISEASE :

This is usually overshadowed by co-existent severe rheumatic deformities of the mitral and aortic valves.Functional tricuspid incompetence is more common than organic disease of this valve, but the distinction can usually only be made at operation. Functional insufficiency is treated by annuloplasty rather than by valve replacement. Tricuspid valve replacement is nearly always performed in conjunction with replacement of left-sided heart valves.

INDICATIONS FOR HEART VALVE REPLACEMENT AT GROOTE SCHUUR HOSPITAL

The following are the indications for heart valve replacement for rheumatic valvular disease at Groote Schuur Hospital(29) : (a) Aortic stenosis and/or aortic incompetence plus symptoms. (b) Mitral stenosis is suitable for closed valvotomy if there are class III symptoms and the valve is suitable. The valve should be replaced if there are class III symptoms and the valve is not suitable for valvotomy e.g., if it is severely calcified. (c) Mitral incompetence with class III symptoms on medical treatment. (d) Asymptomatic patients with aortic incompetence and mitral incompetence may need valve replacement if there are signs of increasing left ventricular dilatation. Most valve replacements at Groote Schuur Hospital are done because of rheumatic heart disease. Table 3.5 indicates the numbers of patients who had prosthetic heart valves implanted at Groote Schuur Hospital between 1962-1982, the types of prostheses inserted and the autopsy rate.

Numerous reports deal with the indications for heart valve replacement in valvular heart disease. While some papers

consider the general indications for surgery in patients with acquired valvular heart disease (28,30-41), others report miscellaneous diseases necessitating valve replacement e.g., papillary muscle rupture(42-45) ; chordal rupture(46) ; aortic incompetence due to aortic diseases such as syphilitic aortitis(47), sinus of Valsalva aneurysm(48), aortic dissection(49), rheumatoid aortic incompetence(50,51) ; Marfan's syndrome(52,53) ; lupus valvulitis(54) ; Whipple's disease(55) ; ochronosis of the aortic valve(56) ; and endomyocardial fibrosis(57,58). Other reports deal with valve replacement in special groups of patients e.g., children(59-75), the elderly(76-82), patients with infective endocarditis(83-97), and patients with valve prostheses who need re-operation(98-100).

2.CONGENITAL HEART DISEASE.

Decisions as to why, when, how and where to operate on children with congenital heart disease have to be handled on an individual basis by the physician in consultation with the parents(101). The doctor has to make a firm recommendation which the parents may accept or reject. The clearest indication for operation is a matter of life or death e.g., a newborn child with transposition of the great arteries and an intact ventricular septum. Without operation there is a 90% mortality rate in a few months ; with surgery the survival rate is 90% over the same period. Some cases of transposition with associated hypoplastic pulmonary valve and infundibulum may require use of a valved conduit to link the right ventricle to the distal pulmonary artery. This is usually done as part of a Rastelli operation(102).

Severely symptomatic heart disease treated by a safe surgical procedure is also a fairly straight-forward decision which yields gratifying results. Surgery may also be performed in order to prevent complications e.g., pulmonary vascular

obstructive disease associated with pulmonary hypertension, and central nervous system complications in infants with cyanotic heart disease. Of lesser importance in the antibiotic era is the reduction of the risk of infective endocarditis.

Following on these general comments, I would like to consider some of the specific indications for valve replacement or use of a valved conduit. Although stenosis and infective endocarditis are commonly appreciated complications of the congenitally bicuspid aortic valve, pure severe aortic regurgitation complicating this congenital malformation, unassociated with either stenosis or infection, is not well recognized. Roberts et al.(103) reported 13 patients who required aortic valve replacement due to this type of incompetence. Severe mitral incompetence in symptomatic patients with ostium primum atrial septal defects may require very complex surgical techniques or mitral valve replacement. Attempts have been made to correct complete atrioventricular canal defects by closure of the defect and reconstruction of the atrioventricular valve. Prosthetic valve replacement can be avoided in the overwhelming majority of such patients, but it is sometimes performed(104). Total correction of a truncus arteriosus in infancy(105) involves separation of the pulmonary arteries from the truncus, closure of the resulting defect in the truncus, patch closure of the ventricular septal defect, and reconstitution of right ventricular-pulmonary artery continuity with an external valved conduit. Some patients have required replacement of their truncal valve at the same time as total correction.

Valve replacement is necessary in 10-15% of the cases of congenital mitral valve malformation(106). However, valve replacement is associated with a higher morbidity and mortality compared to valve repairs. Schwarze and Bernhard(107)describe the special pathology of reconstructable or only prosthetically correctable congenital malformations of the mitral valve. The hammock valve describes a situation in which the mitral valve orifice is obstructed by intermixed

chordae and abnormal papillary muscles implanted just underneath the mural leaflet(108). This condition has been described in the literature under a variety of names(106) e.g., mitral arcade(109), obstructive papillary muscles, hypertrophied papillary muscles, and 'typical' congenital mitral stenosis. This condition is difficult to correct by reconstructive techniques and valve replacement is often necessary. Absent papillary muscles rarely gives rise to mitral stenosis. In such a case there are numerous intermixed chordae attached to the ventricular wall with imperforated interchordal spaces. Valve replacement is again often necessary. A parachute mitral valve is one of the commonest causes of congenital mitral stenosis, but it can be corrected by splitting the papillary muscle and fenestrating the interchordal spaces(106). Congenital mitral valve incompetence is usually treatable by reconstructive surgical techniques. The primary lesion may be one of three types : (i) annulus dilatation and deformation, (ii) cleft leaflet or (iii) leaflet defect. Valve replacement is hardly ever necessary. Tricuspid valve replacement may be performed in patients with Ebstein's anomaly(110).

Patients with tricuspid atresia (and normal ventriculo-arterial connections) usually need some form of systemic to pulmonary artery or cavo-pulmonary artery anastomosis in the first few years of life to alleviate progressive hypoxia. In the Fontan procedure(111), the atrial septal defect is closed and the right atrium is anastomosed to the outlet chamber, either directly or by an external conduit(106). As the outlet chamber is expected to act as a ventricle, there is a theoretical advantage in inserting a valve between the right atrium and the outlet chamber. A Fontan-like surgical approach is also applicable to patients with tricuspid atresia, transposition of the great arteries and pulmonary stenosis(105).

An extracardiac valved conduit has been used to treat pulmonary atresia. The conduit is anastomosed to the distal

main pulmonary artery or to its branches and to a right ventriculotomy incision. Double outlet left ventricle and double outlet right ventricle have similar indications for operation:early repair or pulmonary artery banding in infants with high pulmonary blood flow, aorto-pulmonary shunt and subsequent repair using external valved conduit in patients with associated pulmonary or sub-pulmonary stenosis(106).

Transannular outflow tract patches may be used to overcome right ventricular outflow tract obstruction. If such patients have haemodynamically significant pulmonary insufficiency in association with residual pulmonary artery stenosis, pulmonary hypertension from other causes, or associated tricuspid regurgitation, a prosthetic valve can be implanted at the level of the annulus under the outflow patch or a valved conduit may be used(106).

With regard to univentricular hearts, most centres have abandoned the approach of septation of such hearts plus use of a valved conduit to establish continuity between the newly created "right" ventricle and the pulmonary artery. However, this technique may still be applied in the patient with single left ventricle, left-sided infundibular chamber supporting a discordantly connected and laevopositioned aorta, naturally occurring pulmonary outflow tract obstruction, or two functionally normal atrioventricular valves. The likelihood of damage to and the need to replace the abnormal atrioventricular valves, contributed to the high initial mortality of the procedure and to the post-operative morbidity.

C.MATCHING PROSTHESIS TO PATIENT(112-118).

Consideration should be given to the unique concerns of any given patient before a particular prosthesis is chosen. Roberts(112) discusses the choice of a substitute cardiac valve with reference to type, size and surgeon. He regarded

the caged disc prosthesis as the least desirable since it obstructs, it thromboses and disintegrates. The other three types of valve prostheses had more favourable characteristics. Because of its large size, the caged-ball prosthesis might be limited to patients with mainly regurgitant lesions. The tilting disc has favourable haemodynamics and is durable, but long-term anticoagulant therapy is necessary (as with all of the other mechanical valves). The glutaraldehyde-treated porcine xenograft valve lacks the latter disadvantage, but its later durability is suspect and it is unsuitable for use in young patients due to early cuspidal calcification (see Chapter 12). Roberts believes that if the valve replacement is performed in a large,well-equipped medical centre by an experienced surgical team, the operative result is more dependent on the type and size of substitute valve inserted than on the surgeon who inserts the valve.

1.GUIDELINES FOR THE USE OF TISSUE VALVES (BIOPROSTHESES)

Chung(113) has proposed the following guidelines for use of tissue valves for heart valve replacement :

(i) Patients unable to have adequate control of anticoagulation.

(ii) Patients with less than 10 years life expectancy,especially if the patient is older than 60 years of age.

(iii) Women wanting to have children or patients engaged in potentially traumatic activity.

They should not be used in children or in patients receiving dialysis for renal failure(29).

McClung et al.(114) state that although few anatomic complications have been described, the Ionescu-Shiley pericardial bioprosthesis may be more suitable for aortic valve replacement due to its greater flow capacity, whilst the porcine xenograft(116-118) may be more suitable in the mitral position because of anatomical considerations.

2.GUIDELINES FOR THE USE OF MECHANICAL PROSTHETIC VALVES :

(i) Patients aged 35 years or younger.
(ii) Patients on renal dialysis or having disorders of calcium metabolism(113,115,116).
(iii) Patients needing long-term anticoagulation for other indications e.g., atrial fibrillation or past thromboembolism.

The operative mortality rate at Groote Schuur Hospital for implantation of mechanical prostheses is 5% and the 10 year survival figure is 60%(29). The main problems encountered clinically are thromboembolism, acute mechanical failure and anticoagulant-induced haemorrhage.

D.TRENDS IN CARDIAC SURGERY AT THE UNIVERSITY OF CAPE TOWN.

Three reports(119-121) analyse the trends in cardiac surgery at the University of Cape Town for the years 1951-1965 and 1971-1981 :

(i) OPERATIONS FOR ACQUIRED VALVULAR HEART DISEASE BETWEEN APRIL 1951-APRIL 1965(119) :

Closed mitral valvotomy was performed upon 525 patients,with a hospital mortality rate of 6%. Ten percent of patients died up to 12 years after surgery, mainly due to mitral valve disease related heart failure. Restenosis occurred in about 15% of operated patients. Heart valve replacement was still in its infancy at that time and heart valve replacement was carried out on 85 patients using the University of Cape Town prosthesis. There were 15 hospital deaths (18%) and 10 late deaths. Four patients developed infective endocarditis. The main problem was a high incidence of thromboembolism. In those early years valve replacement was

only performed in desperately ill, often pre-terminal patients.

(ii) CONGENITAL HEART DISEASE NEEDING OPEN HEART VALVE SURGERY APRIL 1951-APRIL 1965(120) :

Open heart valve surgery was performed on 53 patients with a 26% hospital mortality rate. During the same period complete correction was attempted in 113 patients with Tetralogy of Fallot (12% mortality rate) and 62 patients had ventricular septal defects repaired (10% mortality rate).
No published data are available for the years 1966-1970.

(iii) TRENDS IN CARDIAC SURGERY AT THE UNIVERSITY OF CAPE TOWN 1971-1981 :

Parry et al.(121) reported that a yearly average of 560 cardiac operations was performed (75% for acquired and 25% for congenital heart disease) during this period. The average mortality rate was 6.1% between 1971-1975 and 5.0% between 1976-1981. Although it was the policy of the cardiac surgical unit to perform closed mitral valvotomy whenever the clinical indication is suitable, there was a fall in the number of such operations performed in the later part of the study period. A maximum of 59 closed mitral valvotomies in 1972 fell to a minimum of 7 in 1978. This may reflect more stringent criteria for patient selection for closed valvotomy or greater surgical confidence in obtaining a better result by an open procedure. During the first 5 years of this period mitral valvotomies comprised 20.5% of the total valve operations, but in the second 6-year period it had dropped to 10.2%. The high incidence of rheumatic fever in the Cape Province was reflected in a steady stream of new patients. Patients with malfunctioning heart valve prostheses also contributed to the operating load. A substantial reduction of the hospital mortality associated with valve surgery, from a maximum of

8.3% in 1972 to 2.2% in 1980 was noted. This reduction in mortality is probably related in part to improved methods of myocardial protection (cardioplegia) during valve replacement. Causes of operative and postoperative deaths were not analysed in detail, but Parry et al.(121) believed that there were no significant change in factors relating to mortality throughout the 11-year period. Post-operative myocardial failure remained a significant problem in patients who presented late in the course of their valvular disease for surgery.

During this same period Parry et al.(121) noted that the majority of cardiac surgery performed in children was for correction or palliation of congenital lesions ; operations for valve disease formed only 7-15% of the yearly total.

In our institution, patients who have cardiac valvular prostheses implanted receive anticoagulation (Warfarin) from the evening of the second post-operative day. Those with tissue valves are treated for only 3 months, but with mechanical prosthetic valves indefinite anticoagulant administration is practised with regular assessment of the prothrombin index.

E.TYPES OF PROSTHETIC HEART VALVES IMPLANTED IN PATIENTS AT THE UNIVERSITY OF CAPE TOWN BETWEEN 1962-1982 (see Table 3.5).

(i) TISSUE VALVES.

A total of 33 patients had University of Cape Town formaldehyde-treated, porcine aortic valve xenografts implanted in the mitral position (see Chapter 9). No accurate data regarding post-operative deaths are available, but two of these patients were autopsied at the University of Cape Town (U.C.T.) Pathology Department. According to Schrire and Barnard(119) most of the patients underwent re-operation. One hundred and sixty-three patients received Hancock

bioprostheses ; there were 36 deaths (22.1%) and 9 patients (25% of the fatalities) were autopsied. Carpentier-Edwards bioprostheses were inserted in 704 patients ; there were 101 (14.3%) post-operative deaths and 38 patients (37.6%) were autopsied.

(ii) MECHANICAL VALVES.

Five hundred and twenty patients received University of Cape Town lenticular prostheses. No published data are available regarding the high late post-operative death rate. Ninety-eight of these patients came to necropsy in the U.C.T. Pathology Department. Four hundred and thirty-four patients had Starr-Edwards prostheses implanted ; there were 145 post-operative deaths (33.4%) and 44 of the latter patients (30.3%) were autopsied. One hundred and nineteen patients received Lillehei-Kaster prostheses. Fifty-two patients (43.7%) died post-operatively and 16 (30.8%) were autopsied. Bjork-Shiley prosthetic heart valves were implanted in 126 patients and there were 29 deaths (23%). Fourteen of these patients (48.3%) were autopsied. Three hundred and sixty-five patients received St Jude prosthetic valves and there were 33 post-operative deaths (9.0%), of whom 29 were autopsied (87.9%).

(iii) MIXED PROSTHESES.

Twenty-four patients came to autopsy with more than one different type of prosthetic heart valve implanted in the same heart. These 24 patients had 52 prostheses in situ ; the types of prostheses that were inserted are listed in Tables 14.1 and 14.2 of Chapter 14.

TABLE 3.5 : PATIENTS WITH PROSTHETIC HEART VALVES AT THE UNIVERSITY OF CAPE TOWN (UCT) 1962 - 1982.

TYPE OF VALVE	No. OF PATIENTS	KNOWN POST-OP. DEATHS (%)	AUTOPSIES (AUTOPSY RATE %)
UCT XENOGRAFTS	33	-	2
HANCOCK	163	36(22.1)	9(25)
CARPENTIER-EDWARDS	704	101(14.3)	38(37.6)
UCT LENTICULAR	520	-	98
STARR-EDWARDS	434	145(33.4)	44(30.3)
LILLEHEI-KASTER	119	52(43.7)	16(30.8)
BJORK-SHILEY	126	29(23.0)	14(48.3)
St JUDE MEDICAL	365	33(9.0)	29(87.9)

- indicates no data available. A few fresh aortic homografts and fascia lata valves were also inserted - no data available.

F. AETIOLOGICAL DATA ON 100 CONSECUTIVE VALVE REPLACEMENT OPERATIONS.

One hundred randomly selected patients, who underwent heart valve replacement consecutively at Groote Schuur Hospital in 1973 were analysed with regard to the aetiology of their native valvular disease as recorded in the surgical operation notes, the information on the pathology request form,which accompanied the excised valve, and the pathologist's report after macroscopical and histological examination of the excised valve. These data were compared with one another and I then reviewed the pathological diagnosis of the likely aetiology of the native heart valve disease in the light of the operation note details. The latter information had in most instances not been supplied to the original pathologist who first examined the valve.

Table 3.6 summarizes the results of this investigation. A notable feature was that in 62% of patients the surgeon gave no indication on the pathology request form as to the suspected aetiology of the valvular disease necessitating the operation. In only 15% of patients did the operation notes and the request form agree on the aetiological diagnosis. However, in 13% of cases the request form was more informative than the operation notes.

The pathologist was able to make an aetiological diagnosis in only 35% of the excised valves. This is not surprising since fibrous thickening, distortion or destruction of the normal architecture, and superimposition of thrombus are non-specific findings, which may occur in both congenital and acquired valve lesions. The only feature identifying the acquired lesions histologically is the increased vascularity(9). Since some rheumatic-type valves are very sparsely vascularised, even this histological feature is of dubious specificity(8). On reviewing the operation notes in conjunction with the macroscopical description of the excised valve and the cuspidal histology, I was able retrospectively

to make an aetiological diagnosis in 81% of the excised valves (Table 3.7). The crucial information that enables one to improve the aetiopathological diagnosis from 35% to 81% is that which is contained in the surgical operation notes and pertains to the appearance of the intact valve prior to excision. This information is seldom transmitted to the pathologist who has to examine the valve.

The mitral valve is usually excised in toto and thus its macroscopical morphology may be interpreted by the pathologist and most often it takes the form of a chronic rheumatic-type of deformity. The present study found that very few pathologists were prepared to label severe mitral valve stenosis as a chronic rheumatic-type of deformity ; usually only a description was given without any reference being made as to the likely aetiology. Although there are other rare causes of mitral stenosis e.g., Whipple's disease(123,124), carcinoid syndrome(105), treatment with methysergide(125), Fabry's disease (126), Hurler-Schei syndrome(105), familial pseudoxanthoma elasticum (105), the presence of this lesion pathognomonic of previous rheumatic fever(127).

However, in the case of the aortic valve it is even more important that the pathologist be given a guide as to the appearance of the valve at operation and/or the clinically suspected aetiology of the valvular disease, since the aortic valve is usually removed in a fragmented fashion and it is often not possible for the pathologist to reconstruct the appearance of the intact valve. The 39 aortic valves encountered in this series of 100 consecutive valve replacement operations were received as multiple tissue fragments ranging in number from 1 to 11 pieces per valve. As Davies(8) points out, it is not possible to report meaningfully on one cusp. Each report should note the number of cusps, their shape, the presence of fibrosis or calcification, and whether commissural fusion is present. This is usually easily recognizable, even in a surgically excised valve.

In several instances in which infective endocarditis was the clinical diagnosis, this information was not transmitted to the pathologist. Since there is some evidence(128) that infection of the native heart valve at the time of heart valve replacement may predispose to infection of the prosthetic valve, it is important to alert the pathologist to this possibility, since antibiotics may have muted the inflammation and appropriate stains for micro-organisms may consequently not be performed.

TABLE 3.6 : AETIOLOGICAL DATA ON 100 CONSECUTIVE HEART VALVE REPLACEMENT OPERATIONS

OPERATION NOTES AND REQUEST FORM AGREE	15
REQUEST FORM & PATHOLOGY REPORT AGREE	12
OPERATION NOTES DIFFER FROM REQUEST FORM	
REQUEST FORM MORE HELPFUL	13
REQUEST FORM LESS HELPFUL	4
NO OPERATION NOTE FOUND	6
NO AETIOLOGY ON REQUEST FORM	62
PATHOLOGIST DIAGNOSED AETIOLOGY	35
AETIOLOGY AFTER REVIEW OF OP. NOTES & HISTOLOGY	81

TABLE 3.7 : AETIOLOGICAL DIAGNOSES MADE IN 100 CONSECUTIVE HEART VALVE REPLACEMENT OPERATIONS BY REVIEW OF THE OPERATION NOTES IN CONJUNCTION WITH THE MACROSCOPICAL AND MICROSCOPICAL PATHOLOGY.

1.SPECIFIC DIAGNOSIS MADE :	
CHRONIC RHEUMATIC-TYPE DEFORMITY	67
AORTIC NODULAR SCLEROSIS*	6
SYPHILIS	2
CONGENITAL ABNORMALITY	2
INFECTIVE ENDOCARDITIS	3
FLOPPY VALVE	1
TOTAL	81
2.NO DIAGNOSIS MADE	19

(* = senile calcific tricuspid aortic stenosis)

G. INCIDENCE OF ASCHOFF BODIES IN SURGICALLY REMOVED CARDIAC TISSUE.

The Aschoff body (nodule) in its granulomatous (proliferative) phase is the pathognomonic myocardial lesion of rheumatic fever(129). However, many authorities disagree over what constitutes a typical Aschoff body. Rich and Gregory(130) observed nodular collections of monocytes and a predominance of "Aschoff cells". The latter name was applied to the large cell which may be mono- or multinucleated and has a basophilic cytoplasm. While most observers regarded the Aschoff cell as originating from the cardiac histiocyte (Anitschkow cell)(131,132), others believed that the Aschoff cell was derived from damaged myocardial fibres(133,134). In the 1960 second edition of Gould's Pathology of the Heart(135) it is stated that proliferating connective tissue cells are the dominant feature of the Aschoff body and that Aschoff cells are scanty. In the 1968 third edition of the same book(136) it is recommended that the term °°Aschoff cell" should be discarded because of the differing views on its histogenesis. In the same writing the cardiac histiocyte (Anitschkow myocyte) is recognized as the chief component of the Aschoff body(137). As Ward(138) points out, other definitions reveal further differences of opinion regarding the Aschoff body's characteristic features(139-142). Several of these authors, while agreeing that the Aschoff body is specific to rheumatic carditis, also claim that it should only be diagnosed with strict adherence to their own (differing) histological criteria.

Fassbender(143) stresses the perivascular situation of the classical Aschoff body and states that the adventitial cells swell and become separated and participate in the formation of the granuloma. He states that there are three evolutionary patterns of rheumatic carditis :

(i) The "exudative" variety of the rheumatic process may run a fulminating clinical course, especially in children, with

death from heart failure within 3 weeks. Not a single Aschoff body may be present, only an interstitial fibrinous exudate with large numbers of neutrophiles and occasional lymphocytes. This form may represent a type of Arthus phenomenon.

(ii) The granulomatous (proliferative) form of rheumatic carditis is the classical Aschoff body, the features of which will be described below. Fassbender(143) suggests that fibrinoid is the result of pathologically increased capillary permeability, which may result from the deposition of immune complexes (streptococcal antigens and antibodies which bind complement). The Aschoff body (granuloma) is the morphological expression of a local inflammation associated with a limited exudate. The Aschoff body passes through 4 phases : (a) exudative, (b) granulomatous (proliferative), (c) resolving and (d) healed phases. It is only the granulomatous phase which is diagnostic of rheumatic fever. This phase is noted one month or more after an acute attack of rheumatic fever and may persist in the tissue for 3-6 months or even longer after the symptoms of the acute attack have abated(105).

A small area of fibrinoid necrosis may be present at the centre of the nodule in the early granulomatous phase. It becomes surrounded and finally replaced by histiocytes, giant cells, lymphocytes, plasma cells and fibroblasts arranged in roughly parallel rows. The histiocytes (so-called Anitschkow "myocytes") have a characteristic owl's eye appearance to the nucleus due to a bar-like arrangement of the chromatin. These cells give rise to giant cells (Aschoff cells) which are usually found towards the centre of the nodule.

(iii) The muscle-associated ("myo-aggressive granuloma") spares the connective tissue, is usually not seen in association with typical Aschoff nodes and is found in the myocardium itself or in the loose sub-endothelial tissues in juxtaposition to necrotic myofibres. No fibrinoid is seen, only small fragments of necrotic muscle. Auto-antibodies directed against cardiac muscle may cause the necrosis, which may be a late complication of long-continued rheumatic

carditis. The granulomata produced experimentally in rabbit hearts by Murphy(144,145) who repeatedly injected the animals with killed group A Streptococci appear to be of a similar nature to the muscle-associated granuloma and are unlike the Aschoff body. No experimental model of a connective tissue lesion related to small myocardial vessels has yet been produced.

Since rheumatic fever is such an important cause of valvular heart disease in Cape Town, I decided to investigate the incidence of the granulomatous phase Aschoff bodies (as described above) in atrial appendages removed during heart valve surgery. Two groups of patients were studied :

1. One hundred consecutive patients who underwent heart valve replacement comprised the first group. Their atrial appendages, papillary muscles and valves were examined histologically for granulomatous phase Aschoff bodies.
2. The second group consisted of 468 patients who had atrial appendages excised between the years 1973-1982 inclusive at the time of surgery for mitral stenosis or mixed mitral valve disease in which stenosis predominated. The incidence of Aschoff bodies as diagnosed by a variety of pathologists in this group of patients was recorded. I then reviewed the histology of those patients in whom Aschoff bodies had been diagnosed. (See Methodology, section 3 G).

Table 3.8 summarizes the findings in the first group of patients. Atrial appendages were sent for pathological examination in 58% of these patients and proliferative phase Aschoff bodies were seen in 10.3% of the atrial appendages (and in 11.3% of patients with a suspected rheumatic aetiology for the valvular disease). The papillary muscles had been removed as part of the mitral valve excision and examined histologically in 34 patients, only one of whom showed an Aschoff body in this situation(2.9%). In only one out of the 100 patients did a valve cusp contain Aschoff bodies. This accords with the experience of Edwards et al.(146) who found no Aschoff bodies in 34 valves with active valvulitis of

patients who had active rheumatic carditis (myocardial Aschoff bodies perivascularly). These authors believe that non-specific oedema, leukocytic infiltration and fibrinous vegetations are the usual changes of active rheumatic valvulitis.

TABLE 3.8 : INCIDENCE OF PROLIFERATIVE PHASE ASCHOFF BODIES IN 100 CONSECUTIVE VALVE REPLACEMENT OPERATIONS

TOTAL No. OF ATRIAL APPENDAGES	58
APPENDAGES OF CLINICALLY RHEUMATIC PATIENTS	53
APPENDAGES OF NON-RHEUMATIC PATIENTS	5
APPENDAGES CONTAINING ASCHOFF BODIES	6
VALVES CONTAINING ASCHOFF BODIES	1
PAPILLARY MUSCLES CONTAINING ASCHOFF BODIES	1

One hundred and sixteen out of the 468 atrial appendages of patients with mitral valve stenosis (with or without mild incompetence) were recorded as containing Aschoff bodies (24.8%). These diagnoses had been made by several different pathologists, all of whom had ostensibly been looking for granulomatous (proliferative) phase Aschoff bodies. Table 3.9 summarizes my findings after reviewing the atrial appendicular histology of these 116 patients.

TABLE 3.9 : REVIEW OF 116 SURGICALLY REMOVED ATRIAL APPENDAGES (FROM PATIENTS WITH MITRAL STENOSIS) DIAGNOSED BY A VARIETY OF PATHOLOGISTS AS CONTAINING ASCHOFF BODIES

No. OF PTS.	GRANULOMATOUS PHASE ASCHOFF BODIES	REVIEW NEGATIVE FOR ASCHOFF BODIES		
		MONONUCLEAR CELLS	NON-SPECIFIC GRANULOMA	ORGANIZING THROMBUS
116	82	25	4	5

I found that if strict criteria were applied and if only granulomatous phase Aschoff bodies as described earlier above were accepted, then only 82 out of the 116 patients had acceptable Aschoff bodies ; this corresponds to 17.5% of the total group of 468 patients. The commonest error appeared to be the labelling of focal collections of mononuclear cells (mainly lymphocytes) as Aschoff bodies. Four patients had muscle-associated granulomata of the type described by Fassbender(143) without typical Aschoff bodies. Organizing endocardial thrombi were misinterpreted as Aschoff bodies in 5 other patients.

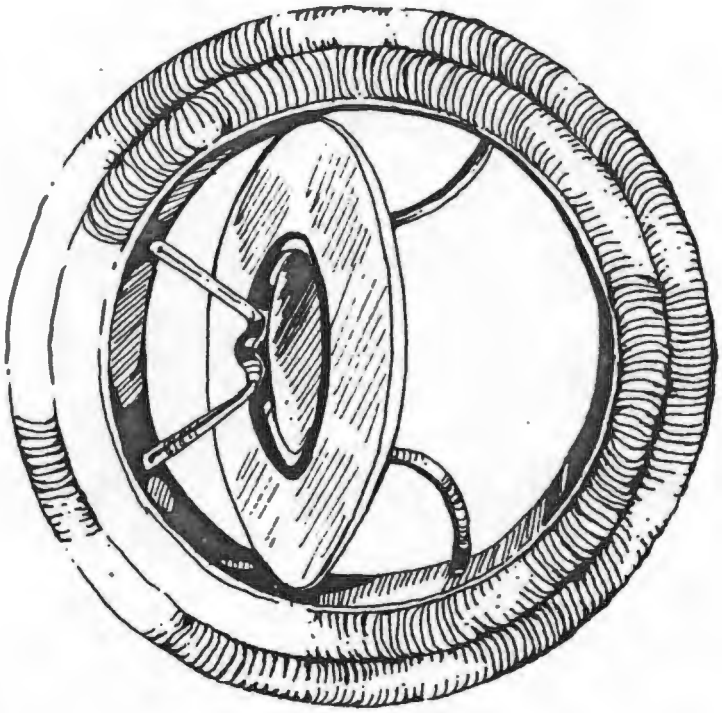
The reported incidence of active Aschoff bodies in atrial appendages removed from patients with mitral stenosis varies from centre to centre (Table 3.10). While all record the incidence of "Aschoff nodules", there are some differences in the histological criteria. Another factor is the variation from centre to centre of the types of patient selected for operation. Most series give little information in this regard. The present study found an Aschoff body incidence of 24.5% when diagnosed by a variety of pathologists and a lower incidence of 17.5% on review by the present author. The Cape Town incidence correlates best with the incidences of 25% reported by Waaler(148) and the 21% noted by Roberts and Virmani(127).

TABLE 3.10 : INCIDENCE OF ASCHOFF BODIES IN ATRIAL APPENDAGES OF PATIENTS OPERATED UPON FOR MITRAL VALVE DISEASE

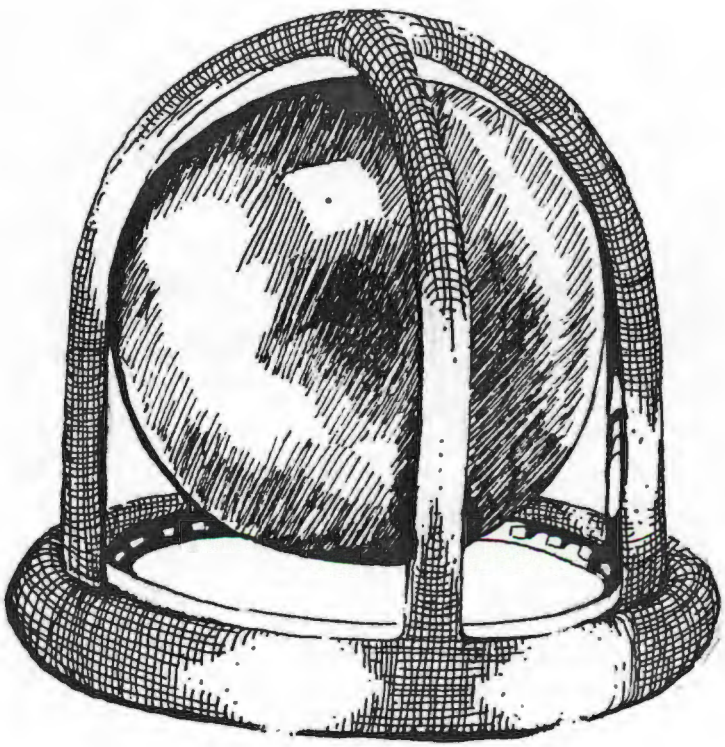
AUTHORS	YEAR	REF. No.	INCIDENCE (%)
PINNIGER	1951	147	67
WAALER	1952	148	25
DECKER et al.	1953	149	46
McKEOWN	1953	150	45
McNEELY et al.	1953	151	46
GIL et al.	1955	152	75
LANNIGAN	1961	153	64
RUEBNER & BOITNOTT	1961	154	41
ROBERTS & VIRMANI	1977	127	21
SILVER	1983	105	40
VIJAYANAGAR et al.	1983	155	2
PRESENT SERIES			18

INCIDENCE OF ASCHOFF BODIES IN AUTOPSIED PATIENTS WITH IMPLANTED VALVULAR PROSTHESES.

In the present study, only 23 out of 272 patients (0.9%) with implanted prosthetic heart valves showed Aschoff bodies histologically in the myocardium. This figure is unduly low since the 272 patients includes some who were operated upon for non-rheumatic valvular heart disease. Since 198 out of the 272 patients (73%) had their valves replaced because of chronic rheumatic valvular deformities, the true incidence is 11.6%. The latter figure is in agreement with the incidence of Aschoff bodies in 10.3% of surgically resected right atrial appendages of such patients. The slightly higher incidence at autopsy compared to biopsy may be related to the more extensive histological sampling which is performed in the autopsy heart.



MECHANICAL VALVES



CHAPTER 4.

PATHOLOGY OF CARDIAC VALVE REPLACEMENT WITH THE UNIVERSITY OF CAPE TOWN CARDIAC VALVE PROSTHESIS

CHAPTER 4.

PATHOLOGY OF HEART VALVE REPLACEMENT WITH THE UNIVERSITY OF CAPE TOWN CARDIAC VALVE PROSTHESIS.

The clinical and haemodynamic findings in patients with University of Cape Town (UCT) valvular prostheses have been previously reported from our institution(1-6) and the pathology of aortic valve replacement with this prosthesis has also been described(7). Details regarding the structure of the UCT aortic and mitral valve prostheses are given in Chapter 2.

AORTIC VALVE REPLACEMENT

The present study reviews the autopsy findings in 41 patients with UCT aortic valve prostheses. There were 34 men and 7 women, with a mean age of 44.5 years (range 16-66 years). Post-operative survival ranged from 7 hours to 141 months. Pre-operatively all patients had been in functional classes III or IV of the New York Heart Association classification. Twenty patients died 30 days or less after operation (group 1,early deaths), and 21 patients died more than 30 days after surgery (group 2,late deaths).

The following diseases (Table 4.1) necessitated aortic valve replacement : 30 patients had a chronic rheumatic-type deformity of the aortic valve and in 16 patients this could be ascribed to rheumatic fever on the basis of either a previous history of rheumatic fever, associated mitral stenosis or Aschoff bodies in the myocardium. The aetiology was uncertain in the other 14 patients. The remaining 11 patients had the following native aortic valve diseases : infective endocarditis 1, calcified congenital bicuspid aortic valve 3, syphilitic aortitis 2, aortic incompetence associated with aortic medionecrosis 3, and 2 had aortic nodular sclerosis (tricuspid senile calcific aortic stenosis). All patients

received anticoagulation (Coumadin) post-operatively.

TABLE 4.1 : NATIVE AORTIC VALVE DISEASE LEADING TO AORTIC VALVE REPLACEMENT WITH UNIVERSITY OF CAPE TOWN AORTIC VALVE PROSTHESIS IN 41 PATIENTS

CHRONIC RHEUMATIC-TYPE DEFORMITY	30
INFECTIVE ENDOCARDITIS	1
CALCIFIED CONGENITAL BICUSPID VALVE	3
SYPHILITIC AORTITIS	2
AORTIC MEDIONECROSIS	3
AORTIC NODULAR SCLEROSIS	2

TABLE 4.2 : PRINCIPAL CAUSES OF DEATH (1 PER PATIENT)IN 41 PATIENTS WITH UNIVERSITY OF CAPE TOWN AORTIC VALVE PROSTHESIS

GROUP 1	
UNKNOWN	7
MYOCARDIAL FAILURE	7
INFECTED PROSTHESIS	3
MYOCARDIAL PERFUSION ERROR	1
PNEUMONIA	1
RUPTURED AORTOTOMY WOUND	1
GROUP 2	
THROMBOEMBOLISM	6
MYOCARDIAL FAILURE	3
INFECTED PROSTHESIS	3
UNKNOWN	3
ANTICOAGULANT EXCESS,BLEEDING	1
AIR EMBOLISM	3
AORTIC RUPTURE (MEDIONECROSIS)	1
DETACHED PROSTHESIS	1

GROUP 1.

Table 4.2 lists the principal causes of death in the short-time survivors with U.C.T. aortic valve prosthesis and Table 4.3 gives the non-fatal complications/associated conditions. There were no complications due to an error in pre-operative diagnosis or operative technique relative to cardio-pulmonary bypass or insertion of the prosthesis. However, myocardial damage was encountered in 4 patients. This took the form of left ventricular contraction band necrosis (coagulative myocytolysis)(8) in a patient who died 20 hours post-operatively,and focal left ventricular colliquative myocytolysis(8) in 2 patients (who survived 7 and 8 hours after surgery). The fourth patient showed subendocardial coagulative necrosis of the left ventricle. None of these 4 patients had significant coronary arterial disease and there was no evidence that the myocardial injury was caused by emboli,iatrogenic damage to the coronary arteries,or due to direct surgical trauma. The myocardial injury appeared to be attributable to poor myocardial perfusion during cardiopulmonary bypass, since there was no history of post-operative hypotension in these patients. The first three of these patients died suddenly and unexpectedly.

Another patient died 5 days post-operatively because of regional transmural coagulative necrosis of the left ventricle. This patient had an unsuspected congenital abnormality of the left coronary artery, which divided almost immediately after its origin into the anterior descending and the left circumflex branches.The result of this unrecognized abnormality was that the coronary perfusion cannula was directed solely into the circumflex branch during surgery and there was no flow of perfusant into the occluded anterior descending branch. At autopsy a reperfusion type of haemorrhagic infarction of the left ventricle was found,which corresponded to the territory of supply of the underperfused anterior descending coronary artery.

Three patients developed infection of their prosthetic valves ; this was due to fungi in two instances (Candida albicans and an unidentified fungal species) and Diphtheroids in the third patient. Massive intracerebral haemorrhage (due to ruptured mycotic aneurysm or embolism) was the terminal event in all 3 patients. Apart from one patient with a coronary thrombo-embolus, post-operative systemic embolism was not encountered in the group 1 patients. No patient in this group had non-infected prosthetic valve thrombi at autopsy. Serious post-operative complications were encountered in 8 patients : 7 had severe myocardial failure, and 1 patient developed bilateral confluent bronchopneumonia.

One complication unique to cardiac surgery was encountered in a patient who underwent aortic valve replacement for annulo-aortic ectasia due to aortic medionecrosis. A corrugated Dacron tube graft was inserted in place of the ascending aorta. Death occurred on the 22nd post-operative day when the distal anchoring sutures of the tube graft tore out of the fragile aortic tissue. Seven patients died suddenly and unexpectedly of unknown causes in the early post-operative period, possibly as a result of a serious cardiac arrhythmia. Changes in the 7 patients who died of unknown cause included the following : serum potassium excess (1 patient), subendocardial ventricular necrosis (4 patients), and interruption of a fascicle of the left bundle branch by a surgical suture (1 patient). Two patients showed no abnormality likely to cause arrhythmia. All 7 patients who died of myocardial failure had only grades 1-2 coronary arterial luminal narrowing. The myocardium showed focal fibrosis in 3 cases and confluent fibrosis in 4. One patient had numerous myocardial Aschoff bodies. The latter were found in the heart of only one other patient in group 1.

Figure 4.1 : Partial dehiscence of a UCT mitral valve prosthesis. There is an unusual lack of host tissue overgrowth on the sewing ring despite the 12 year implantation period.

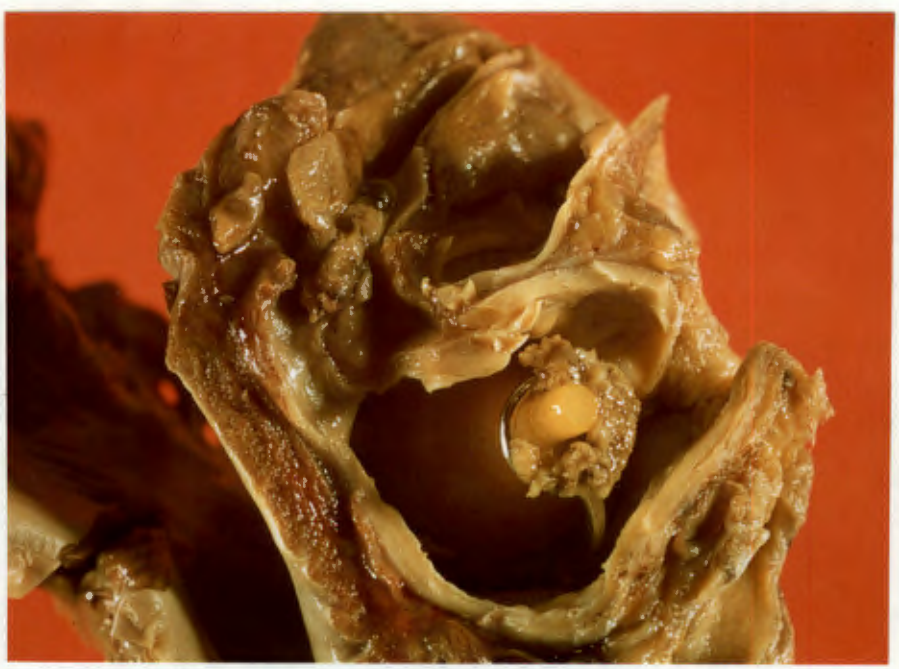


Figure 4.2 : Non-infected thrombus rests upon upper retaining ring of a UCT aortic valve prosthesis. Thromboembolus lies within the left coronary artery (top left).

GROUP 2.

The principal causes of death (1 per patient) in patients who survived more than one month following insertion of a U.C.T. aortic valve prosthesis are listed in Table 4.2. Two of the patients who died in this later period succumbed to complications following intra-operative air embolism and one patient died of air embolism during cardiac catheterization 30 months post-operatively. Three patients developed infection of the prosthesis : an Actinobacillus and Diphtheroids were cultured in 2 patients,but no growth was obtained from the third case. Dehiscence of the prosthesis (Fig. 4.1) unassociated with infection caused the death of one patient. (Mild prosthetic dehiscence in another patient played no significant role in the fatal outcome). Both of these patients were noted to show significant haemolysis. Poor anticoagulation control caused fatal cerebral haemorrhage in one patient.

Thromboembolism, myocardial failure, infection and sudden death (? arrhythmia) were the commonest principal causes of death. None of the 3 patients who died of myocardial failure had acute myocardial lesions detectable by light microscopy. One patient had syphilitic coronary ostial stenosis plus focal myocardial fibrosis. A second patient had Marfan's syndrome with poor pre-operative myocardial function. He was treated successfully for post-operative infective endocarditis, but died of myocardial failure 30 months post-operatively. His myocardium showed confluent fibrosis, and the small coronary arteries contained organizing thrombo-emboli. The third patient, a porphyric subject, had also been treated post-operatively for infective endocarditis. Focal myocardial fibrosis was present and some small coronary arteries contained atheromatous emboli.

Non-fatal complications/associated conditions observed in this group of patients are indicated in Table 4.3. The

silicone emboli appeared to result from inadequate filtration of the silicone, which was used as an antifoam agent in the bubble oxygenator of the cardio-pulmonary bypass machine. Although only 12 patients showed thrombi on their prostheses, there was autopsy evidence of systemic thromboembolism in 15 patients (please see Table 4.4).

TABLE 4.3 : NON-FATAL COMPLICATIONS/ASSOCIATED CONDITIONS IN 41 PATIENTS WITH U.C.T. AORTIC VALVE PROSTHESIS

GROUP 1	
ACUTE RHEUMATIC FEVER	2
ACUTE TUBULAR NECROSIS	1
SUBARACHNOID HAEMORRHAGE	1
HAEMORRHAGE IN RIGHT BUNDLE BRANCH	1
GROUP 2	
MITRAL STENOSIS	3
JEJUNAL CARCINOID TUMOUR	1
PROSTHETIC DEHISCENCE	1
CLINICALLY APPARENT HAEMOLYSIS	2
75%+ CORONARY ARTERY NARROWING	1
SILICONE & ATHEROMATOUS EMBOLI	1

TABLE 4.4 : SITES OF THROMBUS DEPOSITION UPON UCT AORTIC AND MITRAL VALVULAR PROSTHESES

	AORTIC	MITRAL
NO. PATIENTS WITH UCT VALVES	41	36
NO.UCT VALVES WITH THROMBI	13(32%)	12(33%)
SEWING RING : INFLOW ASPECT	2(5%)	6(17%)
OUTFLOW ASPECT	7(17%)	1(3%)
BOTH ASPECTS	6(15%)	2(6%)
METAL GUIDES FOR BOBBIN	5(12%)	2(6%)
BOBBIN	3(7%)	3(8%)

COMBINED FINDINGS IN THE 41 PATIENTS WITH UCT AORTIC VALVULAR PROSTHESIS

HEART WEIGHTS

Table 4.5 gives the heart weights in three groups of operated patients with UCT aortic valvular prostheses. The heaviest hearts were those belonging to patients who had pre-operative aortic valve incompetence.

TABLE 4.5: MEAN HEART WEIGHTS IN THREE GROUPS OF PATIENTS WITH U.C.T. AORTIC VALVE PROSTHESES

PRE-OPERATIVE LESION		MEAN HEART WT.(G) +/-S.D.
AORTIC INCOMPETENCE	(N= 6)	817+/-188 a,b
AORTIC STENOSIS	(N=16)	604+/-121 a
AORTIC STENOSIS/INCOMPETENCE	(N=12)	654+/-192 b

a = p less than 0.05
b = p less than 0.05

The mean heart weight of all patients with UCT prostheses was 710 g (range 343-1124 g). There was no significant difference in heart weight between patients and controls with aortic stenosis. Patients with pre-operative aortic incompetence had significantly heavier hearts than did controls (p less than 0.0001).Patients who died post-operatively of myocardial failure had a mean heart weight of 766 g (range 561-940g). Twenty-nine patients who died of other causes had a mean heart weight of 690 g (range 343-1124 g). The difference in heart weight was not significant between

these 2 groups.

ASCHOFF BODIES : Only 4 of the 30 patients (13%) with chronic rheumatic-type valvular deformity who underwent aortic valve replacement showed Aschoff bodies, while 8 of 44 non-operated controls with rheumatic-type aortic valve deformity had Aschoff bodies (18%). (See too Chapter 3).

SMALL CORONARY ARTERY DISEASE : Fourteen of the operated patients showed abnormalities of their intra-myocardial coronary arteries. Intimal fibrous thickening, medial hypertrophy and thrombo-embolism were the commonest alterations. Two patients had particles of silicone antifoam from the heart-lung machine in small coronary arteries. Control subjects had fewer abnormalities. (See too Chapter 17).

AORTIC ROOT AND PROXIMAL CORONARY ARTERIES : One patient had slight intimal thickening of the aortic root, but the latter was normal in all of the other patients. No significant difference was found in the degree of narrowing of the proximal portions of the two major coronary arteries between patients with UCT aortic valve prostheses and unoperated controls with aortic valve disease. Coronary cannulation injury was thus not demonstrated in the operated patients.

STRUCTURAL ALTERATIONS WITHIN THE PROSTHESIS : The bobbin of the early-model UCT prosthesis accumulated lipid (Fig. 4.3) and acquired an opaque, yellow appearance (variance). This was not noted in prostheses which had been in situ for less than 2 years. Subsequent alterations in the curing technique of the Silastic bobbin during manufacture prevented this change. Noticeable wear of the contact surface of the bobbin was encountered in 2 patients. None of the prostheses showed significant cloth wear.

ORGAN INFARCTS : The distribution of organ infarcts in

patients and controls is indicated in Table 4.6. Organs most commonly bearing infarcts were the kidneys, spleen, heart and brain ; pulmonary infarction was more common in controls, due to associated congestive heart failure. In controls with uncorrected aortic valve disease, systemic emboli (organ infarcts) were found in 36% and pulmonary emboli in 16%. No source of systemic embolism was found in 10 out of the 27 patients (37%) with organ infarcts. The likely source of the emboli in the 17 control patients in whom a potential source was discovered was as follows : infective endocarditis 7 patients, left ventricular thrombi 5, and left atrial thrombi 4 ; one patient had both a left atrial thrombus and left-sided infective endocarditis. The distribution of thrombi on the various portions of the UCT aortic valve prosthesis in the 41 patients studied is given in Table 4.4.

Fig. 4.3 : Early model UCT atrioventricular prosthesis shows bobbin wear and lipid accumulation (variance). The crack in the upper surface of the bobbin is better seen in the lower picture.

TABLE 4.6 : ORGAN INFARCTS IN PATIENTS WITH UCT AORTIC PROSTHESES AND CONTROLS WITH VALVULAR DISEASE

		KIDNEY (%)	SPLEEN (%)	HEART (%)	BRAIN (%)	GUT (%)	LUNG (%)	OTHER (%)
AS	PATIENTS(N=6)	50	33	17	33	0	0	0
	CONTROLS(N=25)	24	20	28	12	8	32	8
AI	PATIENTS(N=18)	33	28	22	6	11	6	0
	CONTROLS(N=29)	35	28	4	14	0	17	7
AS/ AI	PATIENTS(N=16)	31	25	19	25	6	6	19
	CONTROLS(N=22)	23	18	5	0	0	27	0

(AS=aortic stenosis, AI=aortic incompetence)

MITRAL VALVE REPLACEMENT

Thirty-six patients who each had isolated mitral valve replacement with a University of Cape Town (UCT) mitral valve prosthesis were studied. As will be seen from Table 4.7, chronic rheumatic-type deformity of the mitral valve was by far the commonest indication for mitral valve replacement in these 36 patients. However, only 3 out of the 36 hearts contained Aschoff bodies at autopsy. Three patients had non-rheumatic valvular disease.

TABLE 4.7 : NATIVE MITRAL VALVE DISEASE IN 36 PATIENTS LEADING TO VALVE REPLACEMENT WITH A U.C.T. PROSTHESIS

CHRONIC RHEUMATIC-TYPE DEFORMITY	33
FLOPPY MITRAL VALVE	2
INFECTIVE ENDOCARDITIS	1

GROUP 1

The 12 patients in group 1 (who died 30 days or less after valve replacement) had a mean age of 49 years (S.D.= 9), with a range of 28-60 years. There were 7 females and 5 males. The mean post-operative survival period was 7.2 days (S.D.= 8.5),with a range of from a few hours to 21 days. The mean heart weight was 648 grams (S.D.= 265). The principal causes of death in the group 1 patients are given in Table 4.8. Four patients had complications attributable to an error in operative technique ; air embolism occurred in 2, one patient had two sewing ring sutures which penetrated the circumflex branch of the left coronary artery and the fourth patient had severe limitation of prosthetic bobbin movement by the proximity of the inter-ventricular septum (prosthetic disproportion due to a too small left ventricle). Three

patients developed embolic cerebral infarction. One patient had an infection on the prosthesis (Klebsiella species). Four patients died of unknown causes. Few non-fatal complications or associated conditions were observed (Table 4.9).

TABLE 4.8 : PRINCIPAL CAUSES OF DEATH (1 PER PATIENT) IN 36 PATIENTS WITH U.C.T. MITRAL VALVE PROSTHESIS

GROUP 1	
UNKNOWN	4
CEREBRAL THROMBOEMBOLISM	3
AIR EMBOLISM	2
PROSTHETIC DISPROPORTION	1
SUTURES IN CORONARY ARTERY	1
INFECTED PROSTHESIS	1
GROUP 2	
THROMBOEMBOLISM	9
INFECTED PROSTHESIS	4
THROMBOSED PROSTHESIS	3
MYOCARDIAL FAILURE	2
UNKNOWN	2
ANTICOAGULANT EXCESS,BLEEDING	1
PROSTHETIC DEHISCENCE	1
UNRELATED TO CARDIAC SURGERY	1
CATHETERIZATION ACCIDENT	1

GROUP 2

These patients (who survived more than 30 days post-operatively) numbered 24 persons and their mean age was 49 years (S.D.= 14). Fourteen of the patients were females. Mean post-operative survival was 951 days (S.D.= 1314) with a range of 30-6120 days. The mean heart weight in group 2 was

650 grams (S.D.= 232). The principal causes of death in the group 2 patients are listed in Table 4.8. Thromboembolism was the commonest complication encountered. Infection of the prosthesis was encountered in 4 patients. (Staphylococci were involved in 3 cases and no organism was identified in the fourth patient). One patient had a complication related to post-operative cardiac catheterization ; the catheter perforated an iliac artery, which necessitated a laparotomy. The patient then developed severe bilateral bronchopneumonia and died. One patient developed a fatal cerebral haemorrhage due to poor anticoagulation control. Other fatal complications included thrombotic immobilization of the prosthesis, myocardial failure, death unrelated to cardiac surgery (complications following cholecystectomy) and dehiscence of the prosthesis. Cause of death was unknown in 2 patients. The sites of thrombus deposition on the various portions of the UCT mitral prosthesis in the 36 patients (combined groups 1 and 2) are indicated in Table 4.4. Table 4.10 gives the pattern of organ infarcts in the same patients.

TABLE 4.9 : NON-FATAL COMPLICATIONS/ASSOCIATED CONDITIONS IN 36 PATIENTS WITH U.C.T. MITRAL PROSTHESIS

GROUP 1	
ACUTE GASTRIC EROSIONS	1
AORTIC VALVE DISEASE	4
TRICUSPID VALVE DISEASE	1
GROUP 2	
PEPTIC ULCER	2
DIGITALIS TOXICITY	1
BRONCHOPNEUMONIA	2
EMPYEMA	1
GLOMERULONEPHRITIS	1
SILICONE EMBOLI	5
75%+ CORONARY ARTERY NARROWING	1
AORTIC VALVE DISEASE	1
TRICUSPID VALVE DISEASE	5

TABLE 4.10 : ORGAN INFARCTS ENCOUNTERED IN 36 PATIENTS WITH U.C.T. MITRAL VALVE PROSTHESIS

GROUP 1	
BRAIN	4
KIDNEYS	4
SPLEEN	4
HEART	2
LUNG	2
BOWEL	1
LIVER	1
GROUP 2	
KIDNEYS	15
BRAIN	13
SPLEEN	11
HEART	6
LUNG	1
BOWEL	1
LIVER	1
LIMB	1

TRICUSPID VALVE REPLACEMENT

Two patients had isolated tricuspid valves replacement with a University of Cape Town prosthesis. The first patient, a 23-year-old white male, had Ebstein's anomaly of the tricuspid valve plus an atrial septal defect. The patient died of an arrhythmia 24 hours post-operatively and at autopsy the heart weighed 460 grams. No thrombi were seen on the UCT prosthesis which had been well inserted. The second patient was a 19-year-old white female who had had two previous mitral valvotomies because of rheumatic mitral stenosis. She underwent a third mitral valvotomy and her tricuspid valve was

replaced by a UCT prosthesis. Post-operatively she had a shock lung syndrome and septicaemia;death occurred on the fourth post-operative day. Silicone emboli were present in the renal glomeruli and pancreas. The UCT prosthesis showed no abnormality.

MULTIPLE UNIVERSITY OF CAPE TOWN VALVULAR PROSTHESES IN THE SAME HEART

A total of 41 University of Cape Town (UCT) valvular prostheses was implanted in the hearts of 19 patients, who received no other additional kind of heart valve. The sites of implantation of the 41 valves in these 19 patients are indicated in Table 4.11.

TABLE 4.11 : SITES OF IMPLANTATION OF 41 U.C.T. PROSTHETIC HEART VALVES IN 19 PATIENTS

	A,M	A,M,T	M,T
GROUP 1	2	2	2
GROUP 2	10	1	2
TOTAL	12	3	4

A=AORTIC VALVE M=MITRAL VALVE
T=TRICUSPID VALVE

Eighteen of the 19 patients with multiple U.C.T. prostheses had rheumatic fever as the aetiology of their native valvular disease. The remaining patient had a ventricular septal defect and developed infective endocarditis, which caused severe destruction of his aortic and mitral valves.

GROUP 1

These 6 patients comprised 4 females, 2 males ; 3 were coloureds and 3 were whites. Their mean age was 30 years (S.D.= 12) with a range of 16-44 years. The mean post-operative survival period was 5.3 days (S.D.= 11) with a

range of 8 hours to 27 days. The heart weights ranged from 540-1150 grams with a mean of 830 grams (S.D.= 222). Scanty thrombi were present on the sewing ring (inflow aspect) of only 1 out of the 14 prostheses implanted in this group of short post-operative survivors. Infarcts were noted in the following organs : spleen 2 patients, kidneys 4, lung 1, ileum 1, and left ventricle 2. Neither of the latter two patients had significant coronary arterial disease, and the myocardial infarcts were considered to be embolic in origin. The principal causes of death in these patients are indicated in Table 4.12. One is uncertain whether the patient with the aortic dissecting aneurysm developed it at surgery,but death was due to extension of the dissection into both coronary arteries on the 27th post-operative day. One patient had very severe pulmonary stenosis which had been underestimated pre-operatively.

TABLE 4.12 : PRINCIPAL CAUSES OF DEATH (1 PER PATIENT) IN 19 PATIENTS WITH MULTIPLE U.C.T. VALVULAR PROSTHESES

GROUP 1	
MYOCARDIAL FAILURE	2
AIR EMBOLISM	1
DISSECTING ANEURYSM	1
UNRECOGNIZED ASSOCIATED VALVE DISEASE	1
UNKNOWN	1
GROUP 2	
INFECTION	5
MYOCARDIAL FAILURE	3
UNRELATED TO OPERATION (catheterization)	1
THROMBOEMBOLISM	1
THROMBOSED MITRAL & TRICUSPID PROSTHESES	1
ANTICOAGULANT EXCESS,BLEEDING	1
UNKNOWN	1

TABLE 4.13 NON-FATAL COMPLICATIONS/ASSOCIATED CONDITIONS IN 19 PATIENTS WITH MULTIPLE U.C.T. PROSTHESES

GROUP 1	
OTHER VALVE DISEASE	3
SILICONE EMBOLI	2
STONE HEART	1
WOUND INFECTION	1
GLOMERULONEPHRITIS	1
GROUP 2	
GLOMERULONEPHRITIS	1
SILICONE EMBOLI	2
CALCIFIC EMBOLI	1
SUTURE IN BUNDLE OF HIS	1
WOUND INFECTION	1
BOBBIN WEAR	2
75%+ CORONARY ARTERIAL NARROWING	1
PNEUMONIA	1
POST-CARDIOTOMY SYNDROME	1
HYPERTHYROIDISM	1
ACUTE TUBULAR NECROSIS	1
PNEUMOTHORAX	1
OTHER VALVULAR DISEASE	1

GROUP 2

These 13 patients comprised 7 males, 6 females and there were 8 whites, 4 coloureds and 1 black patient. Their mean age was 36 years (S.D.= 8) with a range of 21-52 years. The mean post-operative survival period was 895 days (S.D.= 1066) and the range was 42-3285 days. The mean heart weight was 757 grams (S.D.= 294) with a range of 522-1200 grams. Only three out of the 27 prostheses implanted in these 13 patients showed

any evidence of thrombosis : one patient had abundant base ring thrombus obstructing her U.C.T. mitral and tricuspid prostheses, and another had scanty thrombus on the strut of a mitral prosthesis. Seven prostheses in this group of longer-surviving patients bore infected vegetations. The following organisms were cultured from these 5 patients with infected prostheses : Candida albicans 1, Candida parasilosis 1, Staphylococcus albus 2 and Staphylococcus aureus 1. The following organ infarcts were encountered in these 13 patients : kidneys 9, spleen 7, heart 5, brain 4, lungs 3, liver 1 and ileum 1. Non-fatal associated conditions in the 19 patients with multiple UCT prosthetic valves are listed in Table 4.13.

SUMMARY OF THE PRINCIPAL CAUSES OF DEATH IN THE 98 PATIENTS WITH UNIVERSITY OF CAPE TOWN CARDIAC VALVULAR PROSTHESES

The following groups of principal causes of death were encountered : (a) due to an error in pre-operative diagnosis, 1 ; (b) due to an error in operative technique, 10 (10%) ; due to problems inherent in the cardiac valve prosthesis, 42 (43%) ; (c) post-operative complications, 22 (23%) ; (d) unrelated to the valve replacement operation, 4 (4%) ; and unknown causes, 19 (19%).

COMMENT

The fact that 43% of the deaths were due to problems inherent in the UCT prosthetic valve indicates that the valve is an unsatisfactory prosthesis. With regard to the early deaths following aortic valve replacement it should be noted that the commonest principal causes of death were unknown causes (? arrhythmia) and myocardial failure. The high incidence of myocardial failure in these patients with UCT aortic valve prostheses is probably influenced by poor patient

selection for cardiac surgery. In those early days in which this valve prosthesis was used, cardiac surgery was regarded as a last resort to be used when medical treatment had failed. Many patients were operated upon who would in modern times have either been operated upon earlier in the course of their disease, or they would have been refused surgery because of severe myocardial dysfunction. Less than adequate myocardial protection during cardiopulmonary bypass may also have played a role in the high incidence of myocardial failure post-operatively, since these operations were performed prior to the institution of cardioplegic myocardial protection. The group 2 patients with isolated aortic valve replacement had thromboembolism, myocardial failure, infection and death due to unknown causes as the commonest causes of demise. Although thrombus deposition was slightly less common on the UCT aortic valves compared to the UCT mitral prosthesis, thromboembolism was still an important complication with the UCT aortic prosthesis. Two of the patients in group 2 died of the late effects of operative air embolism.

In patients with an implanted UCT mitral prosthesis the most important causes of death early post-operatively (group 1) were unknown causes, thromboembolism and operative air embolism. Later deaths (group 2) were most often due to systemic thromboembolism, infection of the prosthesis or massive thrombotic occlusion of the prosthesis. Myocardial failure probably favoured the development of the latter complication in some instances. The frequent incidence of thrombus deposition in relation to the UCT prosthesis is reflected in the numerous organ infarcts which were observed at autopsy in these patients. The high thromboembolic rate led to clinical use of the UCT prosthetic being discontinued. Patients with UCT prostheses had a higher incidence of small coronary arterial thromboembolism compared to other prostheses (see Chapter 17, part E).

CHAPTER 5.

PATHOLOGY OF CARDIAC VALVE REPLACEMENT WITH THE STARR-EDWARDS BALL-VALVE PROSTHESIS

CHAPTER 5.

PATHOLOGY OF CARDIAC VALVE REPLACEMENT WITH THE STARR-EDWARDS BALL-VALVE PROSTHESIS

STARR-EDWARDS MITRAL VALVE PROSTHESIS

Between January 1970 and June 1976, 332 adult patients underwent isolated mitral valve replacement (with or without tricuspid valve annuloplasty) with a Starr-Edwards prosthesis(1). The operative, in-hospital, or post-operative mortality rate within 30 days of the operation was 8.0%. Twenty-eight percent of these patients had been lost to follow-up by 1975. Thromboembolism was encountered clinically in 15 late survivors, among whom there was fatal embolism in 5, transient embolic symptoms in 4 and minor embolic effects in another 4 (Dr R. Forman, personal communication). The yearly survival and embolism events in all patients with implanted Starr-Edwards cardiac valvular prostheses listed in the computerized records of Groote Schuur Hospital are indicated in Tables 5.1 and 5.2.

Thirty-four patients came to autopsy following mitral valve replacement with a Starr-Edwards prosthetic valve. Fifteen patients died 30 days or less after operation (group 1) and 19 died later (group 2). The mean age of the patients was 35.1 years (S.D. = 15.2). There were 13 males and 21 females. Twelve patients were whites and there were 14 coloureds, 7 blacks and 1 asiatic patient. The mean period of post-operative survival in group 1 was 10 days (S.D.= 9) and that for group 2 was 37.9 months (S.D.= 35.6). Table 5.3 indicates the models of Starr-Edwards prostheses used in these 34 patients. Only cloth-covered valves had been implanted. (For structural differences between the different models of the Starr-Edwards prosthesis please see Chapter 2 and Table 2.2). Few of the autopsied patients had models 6300 and 6310 ; most had model 6320 or model 6400. The mean heart weight in

TABLE 5.1 : YEARLY SURVIVAL AFTER IMPLANTATION OF STARR-EDWARDS PROSTHESES (1976 - 1982)

YRS. AFTER OP.	LIVE PTS.	EVENTS	DEATHS	SURVIVE INCOMPLETE INTERVAL	REMOVED FOR NEW OP.	INTERVAL SURVIVAL PROPOR.	CUMUL. SURVIVAL RATE
0-1/12	80	0	8	0	0	0.900	0.900
1/12-1	69	0	5	3	0	0.926	0.833
1-2	61	0	4	1	0	0.934	0.778
2-3	56	0	2	2	2	0.963	0.749
3-4	50	0	0	0	0	1.000	0.749
4-5	50	0	4	1	0	0.919	0.688
5-6	45	0	3	1	0	0.933	0.642
6-7	41	0	2	4	1	0.948	0.609

TABLE 5.2 : EMBOLISM EVENTS AFTER IMPLANTATION OF STARR-EDWARDS PROSTHESES (1976 - 1982)

YRS AFTER OP.	EVENT-FREE PTS.	EVENTS IN INTERVAL	EVENT-FREE DEATHS	SURVIVE INCOMPLETE INTERVAL	REMOVED FOR NEW OP.	INTERVAL SURVIVAL PROPOR.	CUMUL. EVENT-FREE RATE
0-1/12	62	0	7	0	0	1.000	0.000
1/12-1	52	5	2	1	0	0.901	0.901
1-2	44	4	1	0	0	0.908	0.818
2-3	39	3	1	0	0	0.922	0.754
3-4	35	1	0	0	0	0.971	0.732
4-5	34	7	2	1	0	0.785	0.575
5-6	24	3	1	0	0	0.872	0.501
6-7	20	2	2	0	1	0.892	0.447

TABLE 5.3 : MODELS OF STARR-EDWARDS MITRAL VALVE PROSTHESES IN 34 AUTOPSY PATIENTS

MODEL No.	No. OF PATIENTS
6300	2
6310	3
6320	15
6400	8
UNKNOWN	6

TABLE 5.4 : PRINCIPAL CAUSES OF DEATH (1 PER PATIENT) IN 34 PATIENTS WITH STARR-EDWARDS MITRAL VALVE PROSTHESES

GROUP 1	
UNKNOWN	5
MYOCARDIAL FAILURE	4
SYSTEMIC THROMBOEMBOLISM	3
UNRELATED TO CARDIAC OPERATION	2
INCORRECT PRE-OPERATIVE DIAGNOSIS	1
GROUP 2	
SYSTEMIC THROMBOEMBOLISM	11
THROMBOSED PROSTHESIS (CLOTH WEAR)	3(2)
MYOCARDIAL FAILURE	2
UNRELATED TO CARDIAC OPERATION	2
INFECTED PROSTHESIS	1

the 34 patients was 594 grams (S.D.= 126). Thirty-three out of the 34 patients had mitral valve replacement for chronic rheumatic-type deformities of their native mitral valves. The remaining patient had developed mitral incompetence with minimal stenosis following infective endocarditis.

GROUP 1

From the principal causes of death in the group 1 patients listed in Table 5.4 it is apparent that most often the cause of death was unknown (? arrhythmia), followed in order of frequency by myocardial failure and thromboembolism.

One patient, who died due to an error in pre-operative diagnosis, had been treated elsewhere for a few weeks with an erroneous diagnosis of broncho-pneumonia and no cardiac treatment had been given. She was finally admitted to Groote Schuur Hospital in a moribund state for operation on a suspected cardiac myxoma. The patient did not survive the operation in which the mitral valve was replaced because of the operative finding of severe chronic rheumatic-type mixed valvular disease.

One-third of the group 1 patients had antemortem thrombi on their Starr-Edwards prostheses and 3 patients had evidence of cerebral thromboembolism. Minor complications observed included a small para-prosthetic leak between the sewing ring of the Starr-Edwards valve and the native mitral valve ring in one patient and peripheral silicone emboli from the bubble oxygenator in five patients. Four patients had severe post-operative myocardial failure and a few had pulmonary diseases, including pneumonia, incidental lung cancer and persistent severe passive venous pulmonary hypertension. One patient had myocardial infarction due to coronary arterial atherosclerosis. Table 5.5 shows the non-fatal complications encountered in the group 1 patients. Three patients had inadequate anticoagulant control ; this led to bleeding in 2 and widespread thrombosis in the third patient. A patient with

severe, persistent post-operative pulmonary hypertension showed changes of severe passive venous pulmonary hypertension at autopsy.

GROUP 2

In the group 2 patients (long survivors) it is evident that thrombus formation in relation to the Starr-Edwards prosthesis (Table 5.6) and resultant thromboembolism were the most important complications. In three patients abundant thrombus had led to virtual immobilization of the prosthetic ball. The commonest organs showing infarcts (in descending order of frequency) were the kidneys, brain,spleen, heart and the limbs. Poor anticoagulant control led to a small subarachnoid haemorrhage in one patient. Severe cloth wear (Figure 5.1) over the sewing ring of the prosthesis was recorded in 5 patients with post-operative survival periods varying from 26.5 to 96 months. Myocardial failure occurred in only 2 of the 19 patients.One patient was found to have a fistula between the oesophagus and the left atrium, which was sealed by thrombus. A likely cause of the fistula is that it was caused during the operation by a cautery electrode touching the lead of the intra-oesophageal temperature-monitoring device. One patient developed pneumonia and 2 patients had serious diseases unrelated to the cardiac surgery (endometrial carcinoma, miliary tuberculosis).

The principal causes of death in the 19 group 2 patients are indicated in Table 5.4. Thromboembolism (coronary or cerebral) killed 11 patients and three died of thrombotic obstruction of their prostheses. Thus, seventy-five percent of the late deaths were related to thrombus deposition on the prosthesis. Other miscellaneous causes of death are listed in the same Table.

TABLE 5.5 : NON-FATAL COMPLICATIONS/ASSOCIATED CONDITIONS IN 34 PATIENTS WITH STARR-EDWARDS MITRAL VALVE PROSTHESES

GROUP 1	
INADEQUATE ANTICOAGULATION CONTROL	3
SILICONE EMBOLI	5
MILD PROSTHETIC DEHISCENCE	1
LUNG CARCINOMA	1
BRONCHOPNEUMONIA	1
SEVERE PULMONARY HYPERTENSION	1
LEFT ATRIAL BALL THROMBUS	1
GROUP 2	
ENDOMETRIAL CARCINOMA	1
TUBERCULOSIS	1
SUBAORTIC STENOSIS DUE TO PROSTHESIS	1
POST-OPERATIVE SUBMITRAL FALSE ANEURYSM	1

TABLE 5.6 : SITES OF THROMBUS DEPOSITION ON STARR-EDWARDS MITRAL VALVE PROSTHESES

No. OF PATIENTS WITH STARR-EDWARDS PROSTHESES		34
No. OF PROSTHESES BEARING THROMBI		18
SEWING RING:	INFLOW ASPECT	12
	OUTFLOW ASPECT	3
	BOTH ASPECTS	3
CAGE		8
METAL BALL		1

TABLE 5.7 : ORGANS WITH INFARCTS IN 34 AUTOPSY PATIENTS WITH STARR-EDWARDS MITRAL VALVE PROSTHESES

GROUP 1	
BRAIN	4
KIDNEYS	4
LUNGS	3
LIMBS	2
HEART	2
SPLEEN	1
GROUP 2	
BRAIN	9
SPLEEN	8
HEART	2
LIMB	1
BOWEL	1

GROUPS 1 AND 2 COMBINED

The sites of thrombus deposition on the 18 Starr-Edwards mitral prostheses bearing thrombi are detailed in Table 5.6. The commonest sites were the inflow aspect of the sewing ring and the inner aspect of the cage. The pattern of organ infarcts is indicated in Table 5.7. None of the patients had more than 75% luminal narrowing of a major coronary artery and none had Aschoff bodies in the myocardium.

Figure 5.1 : Removal of abundant thrombus from this Starr-Edwards mitral valve prosthesis revealed cloth wear and loss over much of the base ring due to wear of the protective metal studs on the contact zone of the ring.

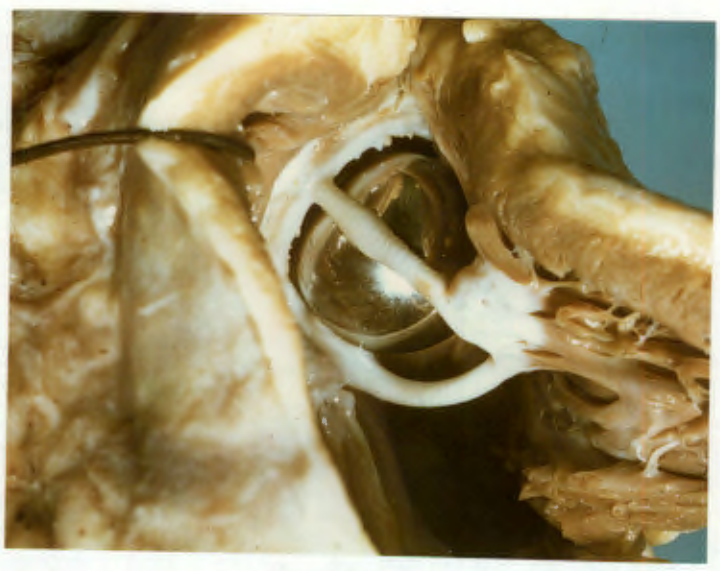


Figure 5.2 : Disproportion between the bulky Starr-Edwards tricuspid prosthesis and a mildly dilated right ventricle has led to incorporation of part of the cage into the right ventricular free wall.

STARR-EDWARDS AORTIC VALVE PROSTHESIS

Only seven patients with isolated Starr-Edwards aortic valve prostheses were autopsied. These patients had a mean age of 46 years (S.D.= 10.1) and a range of 34 to 62 years. There were 6 whites and 1 colcured patient. The pre-operative aortic valvular lesions were as follows : aortic nodular sclerosis (tricuspid senile calcific aortic stenosis) 1, stenotic calcified congenital bicuspid aortic valve 3, rheumatic fever 1 and aortic incompetence secondary to dissecting aneurysm of ascending aorta 1, and unknown 1. The mean post-operative survival period of these 7 patients was 482.4 days (S.D.= 935), with a range of from 0 to 2520 days. Three patients died one month or less following the valve replacement operation. The mean heart weight in the seven patients was 785 grams (S.D.= 359). Six patients received model 2400 Starr-Edwards aortic valve prostheses and one received a model 2320 prosthesis. Three patients had very severe coronary atherosclerosis and 2 of these patients had undergone saphenous vein aorto-coronary arterial bypass grafts at the same time as the valve replacement operation. The coronary arterial narrowing in the third patient was not so severe as to warrant such grafting at the time of operation 7 years before death, but the coronary atherosclerosis had progressed markedly since then and had caused 2 separate myocardial infarcts.

GROUP 1

The principal causes of death (Table 5.8) in 3 patients who survived 30 days or less post-operatively consisted of irreversible, anoxic brain damage in a patient who was separated from the pump for 4 minutes during cardiopulmonary

bypass when the lines became disconnected due to a build-up of pressure in the arterial line ; a ruptured aortotomy wound in a patient with aortic medionecrosis ; and sticking of the prosthetic ball in a patient with a too narrow aortic root. The latter complication had been recognized at surgery, but the aortic patch which had been inserted failed to fully correct the problem. Only one of these 3 group 1 patients had scanty thrombus on the struts of the prosthesis. One cannot comment on systemic embolization, since in two out of the 3 autopsies only the heart was examined (partial postmortems). Other complications noted in these 3 early deaths included acute gastric erosions, excessive anticoagulation, and a pseudomonas gastroenteritis.

TABLE 5.8 : PRINCIPAL CAUSES OF DEATH (1 PER PATIENT) IN 7 PATIENTS WITH STARR-EDWARDS AORTIC VALVE PROSTHESES

GROUP 1	
BYPASS ACCIDENT-INDUCED CEREBRAL ANOXIA	1
RUPTURED AORTOTOMY WOUND (MEDIONECROSIS)	1
PROSTHETIC DISPROPORTION	1
GROUP 2	
INFECTED PROSTHESIS	3
THROMBOSED PROSTHESIS	1

GROUP 2

The 4 patients comprising group 2 all had thrombotic material on their prostheses (rings and cages) ; this was infected in 3 and bland in one patient. Two out of the 3 patients with infective endocarditis had aortic ring abscesses and in only one was there involvement of a natural (mitral)

valve. One patient was infected by Bacillus cereus and another by Staphylococcus aureus. Whilst no organism was cultured from the third patient, gram positive cocci were seen on a smear of the vegetations. Two of the patients with infective endocarditis showed recent septic organ infarcts : cardiac, splenic and renal in one patient and splenic and renal in the other. Silicone emboli from the bubble oxygenator were seen in the glomeruli of one patient. The principal causes of death in these 4 patients (Table 5.8) were infective endocarditis (3 patients) and thrombotic obstruction of the prosthesis in one patient. The development of thrombosis in the latter patient may have been favoured by the ischaemic heart disease-induced myocardial failure from which this patient also suffered. None of these 7 patients showed Aschoff bodies histologically in their hearts.

TWO STARR-EDWARDS PROSTHESES IN THE SAME HEART

Autopsies were performed upon 3 patients who each had 2 Starr-Edwards valve prostheses implanted in their hearts. The salient clinicopathological features in these patients are given in Table 5.9. Patient 1 died of a Pseudomonas pneumonia and lung abscesses. The prostheses of these 3 patients exhibited tissue ingrowth into the cloth covering the sewing ring and base rings. Patient 2 showed a unique form of host tissue ingrowth, whereby portion of the cage of the tricuspid prosthesis became attached to and incorporated into the wall of the ventricle (Fig. 5.2). This complication appeared to result from endocardial trauma produced by the bulky prosthetic cage and organization of thrombus. Ball movement was severely limited by the host pannus and this prosthetic-related complication appeared to have played a significant role in the production of the patient's symptoms of heart failure.

TABLE 5.9 : CLINICOPATHOLOGICAL DATA ON 3 PATIENTS WITH DOUBLE STARR-EDWARDS PROSTHETIC VALVE REPLACEMENTS

	PT.1	PT.2	PT.3
AGE,RACE,SEX	32,W,F	23,C,F	54,W,M
AETIOL.PRE-OP.LESIONS	RHEUM.	RHEUM.	RHEUM.
VALVES REPLACED	M,T	M,T	A,M
POST-OP.SURVIVAL (DAYS)	3	1095	510
CAUSE OF DEATH	PNEUMONIA	AS	C.C.F.
PROSTHETIC THROMBI	M-,T-	M+,T-	A-,M-
TISSUE INGROWTH	M-,T-	M-,T+	A-,M-
STASIS THROMBI	NIL	NIL	LA,LV
HEART WT.(G)	498	680	1208
ASCHOFF BODIES	NIL	+	NIL

A=aortic valve,M=mitral valve,T=tricuspid valve
LA=left atrium,LV=left ventricle,W=white,C=coloured
M=male,F=female,RHEUM=rheumatic fever,AS=aortic stenosis
CCF=congestive cardiac failure,+=scanty,-=absent.

PRINCIPAL CAUSES OF DEATH IN ALL 44 PATIENTS WITH STARR-EDWARDS PROSTHESES

The principal causes of death in the 44 patients with Starr-Edwards valvular prostheses was as follows : (a) due to error in pre-operative diagnosis, 1 ; (b) due to error in operative technique, 2 ; (c) due to problems inherent in the prosthetic valve, 23 ; (d) post-operative complications, 9 ; (e) unrelated to the valve replacement operation, 4 ; and (f) unknown causes, 5.

COMMENT

Starr et al.(2) reported a 10-year follow-up of 290 patients with isolated mitral valve replacement with noncloth- and cloth-covered Starr-Edwards prostheses. The 10-year projection of the percentage of patients alive and free of emboli (disregarding transient ischaemic attacks) for the Model 6310-6320 (50%) was similar to that actually observed for the model 6120 (46%). Salomon et al.(3) compared the long-term results of isolated mitral valve replacement in 897 patients with Starr-Edwards Model numbers 6000 and (49 cases) and 6120 (519 cases) ; aortic allografts (115 patients) and 214 porcine xenograft valves. Thromboemboli were more common with the Starr-Edwards than with either of the tissue valves. Patients with Starr-Edwards Models 6120 and 6000 valves sustained an incidence of fatal thromboemboli of 1.0% and 0.6% per patient-year respectively.Patients with allograft valves suffered an incidence of 0.4% per patient-year. In contrast, no fatal thromboembolism occurred in patients with porcine xenograft valves.

Fraser and Waddell(4) studied 47 patients with isolated aortic valve replacement and found a statistically significant lower incidence of emboli in those who were on °°well-controlled" antocoagulant therapy compared to others who received no anticoagulants. However, Lewis et al.(5) found in their study of the results of aortic valve replacement with the Starr-Edwards prosthesis in 86 patients, that thromboembolism was a major problem. It was noted in 15 patients and was fatal in 5% of patients followed up for 3 years. Herr et al.(6) encountered fatal prosthetic infection in 5 out of 266 patients who had Starr-Edwards valves implanted over a 4-year period. Six patients developed a peri-prosthetic leak, 7 patients had severe anaemia due to haemolysis, and embolism was noted in 27 of 65 patients who had been followed for a minimum of 3 months. Twenty-two out of the 27 patients with emboli had atrial fibrillation.

Roberts and Morrow(7) reported on autopsies performed upon 98 patients with Starr-Edwards valves. In the 65 early deaths (less than 1 month post-operatively) major causes of death included mechanical interference to proper functioning of the prosthesis in 22 patients, uncontrolled bleeding (22 patients), and acute myocardial infarction (16 patients). Less frequent early fatal complications were associated uncorrected valvular disease, pulmonary complications, arrhythmia, and infection. Causes of the 33 late deaths included prosthetic valve infection (in 5 patients), congestive heart failure (8 patients) sometimes due to prosthetic thrombosis, and sudden unexpected death.

Prosthetic valve thrombi were found at autopsy in 27 of the 33 patients and other complications included intimal thickening of the aortic root and proximal portions of the major coronary arteries, traumatic intra-vascular haemolysis, and ball variance. The latter problem is reviewed by Laforet et al.(8) who described a patient whose death resulted from ball variance. They state that 29 out of 1400 Starr-Edwards valves returned to Edwards Laboratories Inc. for examination showed ball variance of some degree. This consisted of change in colour, mass, hardness, shape or surface appearance. Magovern(9) has described a case in which the ball of an aortic valve prosthesis had increased in size to the point where it became stuck in the open position. Similar cases have also been reported by others(10,11). Ball variance has not been encountered at Groote Schuur Hospital since only Starr-Edwards prostheses with metal (Stellite) balls have been used. Hameed et al.(12) described a patient whose Starr-Edwards aortic valve prosthesis suffered ball fracture with extrusion and dissemination of the plastic ball material into the systemic circulation. Gobel et al.(13) reported a patient with fatal coronary arterial embolism resulting from a similar complication.Others have reported similar cases of ball fracture leading to systemic embolism(14).

Cloth wear, as seen in some of my patients and recorded

in the literature(15-18), may be a significant problem. Cloth wear was seen in 5 out of 47 Starr-Edwards prosthetic valves implanted in 44 patients in the present study. All 5 were Model 6310-6320 mitral prostheses in which wearing away of the metal studs had led to subsequent cloth wear. Bonchek and Starr(15) reported cloth wear in 10 patients with Starr-Edwards valves and expressed the hope that the newer model 2400 aortic and 6400 mitral composite track valves would overcome this problem. Shah et al.(16) suggest that the following clinical findings should arouse suspicion of cloth wear : (a) recurrent transient cerebral ischaemic attacks or other systemic emboli despite adequate anticoagulation ; (b) systemic arterial embolization more than 4 years after valve replacement with cloth-covered prostheses ; (c) increase in loudness of the prosthetic valve clicks on auscultation, particularly with a metallic pitch ; (d) persistent severe haemolytic anaemia with or without regurgitation across the prosthesis ; and (e) incomplete seating of the poppet on the valve orifice seen on cinefluorography or intra-valvular regurgitation seen on angiography.

The true incidence of cloth wear in general, and of clinically significant cloth wear in particular, is unknown. Starr et al.(17) reported that 12 out of 18 patients with cloth-covered aortic valve valves (Models 2310-2320) who were re-operated upon for a variety of reasons showed cloth wear. Four of these 12 patients were re-operated upon for haemolytic anaemia and all 4 had strut cloth wear. Isom et al.(18) stated that clinically significant cloth wear was present in 1% of their patients. Shah et al.(16) observed an overall incidence of 2.5% (aortic valve prostheses 3.3% and mitral valve 1.2%). Teflon fibre embolism resulting from cloth wear has been observed at autopsy(19). Sudden death due to fatal coronary arterial obstruction due to Starr-Edwards aortic valve cloth wear has also been reported(20). The composite strut valves do not develop strut cloth wear but, as was observed in my patients, the metal studs that protrude through the sewing

ring cloth may wear away and lead to cloth wear(21).

Ringel et al.(22) reported a unique form of structural failure of a Starr-Edwards aortic track valve,which has not been observed in my study. Fractures of the 3 struts and their liners had occurred above their insertion into the valve ring. At operation the ball was found in the aortic root and the cage was lodged in the descending aorta at the level of the diaphragm. Complete detachment of the entire prosthesis may also occur occasionally(23).

There are numerous reports(5,24-56),including one from our own institution(1), detailing the haemodynamic and clinical findings in patients with Starr-Edwards prostheses. Other papers address more specifically the problems of valve obstruction due to thrombosis(57-62), infection(58,63,64), mitral valve remnants(65) and encroachment by pannus(66,67). Relatively few reports(68-72) give detailed data on the valvular or general autopsy findings in patients with Starr-Edwards valves. Vasconez(73) studied healing around the Starr-Edwards aortic valve replacement in patients and concluded that the Starr-Edwards prosthesis with a Teflon sewing ring is held in place predominantly by sutures and host tissue ingrowth is minimal. This explains why peri-prosthetic leakage has not been uncommon. These authors welcomed the change of the sewing ring of the Starr-Edwards valve from Teflon to Dacron.

Seningen et al.(74) drew attention to the problem of disproportion between the bulky Starr-Edwards ball-valve prosthesis and a too narrow aortic root, which may lead to prosthetic aortic stenosis and death due to too low a cardiac output. Prosthetic stenosis was observed in one of my patients with a tricuspid valvular prosthesis in which a strut had become fused to the ventricular wall by fibrous tissue, probably due to organized thrombus. Engagement of a papillary muscle or the wall of a ventricle by a strut of an open-cage (Cutter) ball-valve prosthesis has also been reported(75).

In 1983, Starr(76) reviewed ball valve prostheses from a

perspective of 22 years. He suggests that the Starr-Edwards mitral Silastic ball-valve,which has been in use for 17 years, is the valve of choice except in very elderly patients and those in whom anticoagulant therapy poses a big risk. Starr also concluded that, overall, there are no major differences in the incidence of thromboembolism between currently available tissue valves and the ball valve during the same time frame (from 1973 onwards). He also claims that the St Jude Medical valve(77,cited reference) has a thromboembolism-free rate comparable to that of the Starr-Edwards Silastic ball-valve. Regarding thrombotic stenosis in aortic valve replacement, he cited evidence to show that the Bjork-Shiley valve was 97% free of this complication at 5 years, whereas the Starr-Edwards ball-valve was 99.5% free. In a recent study(78), in vitro velocity, shear stress, and pressure drop measurements were made under steady-flow conditions and used to interprete some of the failure modes of the Starr-Edwards prostheses as observed at autopsy(79-83).

For further discussion on the pathological findings in my 44 patients with Starr-Edwards prosthetic heart valves please see Chapter 18 (OVERALL REVIEW).

CHAPTER 6.

PATHOLOGY OF CARDIAC VALVE REPLACEMENT WITH THE BJORK-SHILEY TILTING-DISC VALVE PROSTHESIS

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PATHOLOGY OF CARDIAC VALVE REPLACEMENT WITH THE BJORK-SHILEY TILTING-DISC VALVE PROSTHESIS.

Table 6.1 gives the yearly survival for patients who had Bjork-Shiley valvular prostheses implanted at Groote Schuur Hospital. The post-implantation embolism events are summarized in Table 6.2.

AORTIC VALVE REPLACEMENT

Autopsies were performed upon 12 patients with Bjork-Shiley aortic valve prostheses. Seven of the 12 patients were males and there were 7 whites, 4 coloureds and one black patient. The mean age of the 12 patients was 35.2 (S.D.= 15.2) years with a range of 2-60 years. (One patient was 2 years old and the remainder were all older than 25 years). The aetiology of the native aortic valvular disease necessitating valve replacement is given in Table 6.3 ; congenital abnormalities of the aortic valve and rheumatic fever were the commonest underlying pathology.The mean post-operative survival period was 110 (S.D.= 203) days with a range of 0-720 days. The mean heart weight was 579 (S.D.= 192) grams. The 2-year-old child had a heart weight of 115 grams. The heart weights of the other 11 adult patients ranged from 448-907 grams. Only one out of the 12 patients had scanty platelet and fibrin thrombus on the edge of the sewing ring (outflow aspect) of the Bjork-Shiley prosthesis. All patients received an anticoagulant (Warfarin) post-operatively.

Seven of the 12 patients had a forensic autopsy and only the hearts were referred to me for examination.No data are available regarding organ infarcts in these 7 patients. Two out of the 5 patients who had full postmortems showed organ infarcts viz. renal infarcts in 2 and embolic left ventricular myocardial infarction in one. Table 6.4 gives the principal

causes of death (1 per patient) in the patients with Bjork-Shiley aortic valve prostheses.

TABLE 6.1 : YEARLY SURVIVAL AFTER IMPLANTATION OF BJORK-SHILEY PROSTHESES (1976 - 1982)

YRS. AFTER OP.	LIVE PTS.	EVENTS	DEATHS	SURVIVE INCOMPLETE INTERVAL	REMOVED FOR NEW OP.	INTERVAL SURVIVAL PROPOR.	CUMUL. SURVIVAL RATE
0-1/12	182	0	12	0	3	0.934	0.000
1/12-1	160	0	8	8	4	0.948	0.885
1-2	140	0	5	11	1	0.963	0.852
2-3	123	0	9	5	0	0.925	0.788
3-4	109	0	3	6	3	0.971	0.765
4-5	97	0	5	9	2	0.945	0.723
5-6	81	0	4	17	0	0.945	0.683
6-7	60	0	3	17	3	0.940	0.642

TABLE 6.2 : EMBOLISM EVENTS AFTER IMPLANTATION OF BJORK-SHILEY PROSTHESES (1976 - 1982)

YRS. AFTER OP.	EVENT-FREE PTS.	EVENTS IN INTERVAL	EVENT-FREE DEATHS	SURVIVE INCOMPLETE INTERVAL	REMOVED FOR NEW OP.	INTERVAL SURVIVAL PROPOR.	CUMUL. EVENT-FREE RATE
0-1/12	169	3	11	0	3	0.981	0.981
1/12-1	146	4	7	6	3	0.971	0.953
1-2	126	7	4	11	1	0.941	0.897
2-3	103	3	6	2	0	0.970	0.870
3-4	92	1	3	2	2	0.989	0.860
4-5	84	3	1	7	2	0.962	0.827
5-6	71	2	4	16	0	0.967	0.800
6-7	49	1	1	15	3	0.975	0.780

GROUP 1

The 6 patients in this group consisted of 5 whites and 1 black patient ; there were 3 males and 3 females. The mean age was 34 years (S.D.= 19.3) with a range of from 2-60 years. Pre-operative native valvular disease is listed in Table 6.3 and the principal causes of death are given in Table 6.4. The mean post-operative survival period was 2.6 days (S.D.= 3.8) with a range of 0-9 days. The mean heart weight in this group of patients was 566 grams (S.D.= 266) with a range of from 115 to 907 grams. Two group 1 patients died due to an error in pre-operative diagnosis, namely unrecognized very severe (Heath-Edwards grade 6) pulmonary hypertension in one and congenital sub-aortic stenosis in another. Problems with regard to operative technique led to the demise of 2 patients : 1 had severe myocardial damage, so-called °°stone heart" (1) and the other had a shock lung syndrome. There were two general post-operative complications in this group (pneumonia and intrathoracic bleeding).

The non-fatal complications/associated conditions in this group of 12 patients with Bjork-Shiley aortic prostheses are listed in Table 6.5.

GROUP 2

There were also 6 patients in group 2 (who survived more than 30 days post-operatively). They consisted of 4 coloureds and 2 whites ; 4 out of the 6 were males. The mean age was 36.5 years (S.D.= 11.4) with a range of from 25-50 years. The mean post-operative survival was 218 days (S.D.=251) and the range was from 90 to 720 days. The mean heart weight in this group of patients was 595 grams (S.D.= 62) with a range of 540-648 grams. The principal causes of death and associated conditions are given in Tables 6.4 and 6.5. Problems with regard to operative myocardial protection led to one patient

developing the "stone heart" syndrome, (see Chapter 17). An heterotopic heart transplant was attempted using a donor heart from a baboon in order to try and save the patient's life, but the graft functioned for only 4 hours. Another patient suffered dehiscence of the prosthesis. Only one patient had an infected prosthesis (no organism cultured). One patient developed a complication which is unique to open heart surgery, namely post-perfusion coronary ostial stenosis. Two deaths unrelated to operation were rupture of a pre-existing cerebral mycotic aneurysm and a fatal motor vehicle accident. None of the hearts showed Aschoff bodies.

TABLE 6.3 : AETIOLOGY OF THE NATIVE VALVULAR DISEASE IN 12 PATIENTS WITH BJORK-SHILEY AORTIC VALVE PROSTHESES

GROUP 1	
RHEUMATIC FEVER	2
CONGENITAL*	2
AORTIC NODULAR SCLEROSIS	1
AORTIC MEDIONECROSIS	1
GROUP 2	
CONGENITAL**	2
INFECTIVE ENDOCARDITIS	1
UNKNOWN	2
RHEUMATIC FEVER	1

*=AORTIC STENOSIS,TRUNCUS ARTERIOSUS.
**=CALCIFIED CONGENITAL BICUSPID AORTIC VALVE.

TABLE 6.4 : PRINCIPAL CAUSES OF DEATH (1 PER PATIENT) IN 12 PATIENTS WITH BJORK-SHILEY AORTIC VALVE PROSTHESES

GROUP 1	
PULMONARY HYPERTENSION	1
STONE HEART	1
UNRECOGNIZED SUBAORTIC STENOSIS	1
BLEEDING	1
SHOCK LUNG SYNDROME	1
PNEUMONIA	1
GROUP 2	
STONE HEART	1
DEHISCENCE OF PROSTHESIS	1
RUPTURED MYCOTIC ANEURYSM	1
INFECTED PROSTHESIS	1
POST-PERFUSION OSTIAL STENOSIS	1
MOTOR VEHICLE ACCIDENT	1

TABLE 6.5 NON-FATAL COMPLICATIONS/ASSOCIATED CONDITIONS IN 12 PATIENTS WITH BJORK-SHILEY AORTIC VALVE PROSTHESES

GROUP 1	
PUMP LUNG	1
MEDIASTINAL SURGICAL EMPHYSEMA	1
75%+ CORONARY ARTERIAL NARROWING	1
GROUP 2	
EXTRA-DURAL ABSCESS (OTITIS MEDIA)	1
SEVERE HAEMOLYSIS	1
75%+ CORONARY ARTERIAL NARROWING	1
HETEROTOPIC HEART TRANSPLANT (4HRS)	1

MITRAL VALVE REPLACEMENT

1. Only one patient with a Bjork-Shiley mitral valve prosthesis was autopsied. The patient was a 13-year-old black female with rheumatic mitral stenosis and incompetence. In 1978 her mitral valve was replaced with a Carpentier-Edwards bioprosthesis. Cuspidal calcification led to functional stenosis of the latter prosthesis, which necessitated its replacement by a Bjork-Shiley prosthesis. Free-floating thrombus was noted in the left atrium at operation. The patient died at the end of the operation. Autopsy revealed occlusion of the left main coronary artery by a thromboembolus. This patient's death is attributable to the calcification-induced stenosis of the Carpentier-Edwards bioprosthesis. No abnormality of the Bjork-Shiley valve was noted.

2. I have had the opportunity of examining Bjork-Shiley mitral valve prostheses which were surgically removed from 3 patients:

(a) The first patient, a 30-year-old white female, underwent cardiac catheterization because of a para-valvular leak. During the catheterization procedure the disc was dislodged due to the catheter passing through the lesser instead of the greater orifice as had been intended. Emergency mitral valve replacement was performed and the dislodged disc was recovered from the aorta.

(b) The second patient was a 44-year-old coloured female who had a Bjork-Shiley mitral prosthesis inserted 3.5 years before. She then underwent re-operation because of severe aortic stenosis and at surgery it was noted that host pannus had grown over the base ring and narrowed the effective orifice of the Bjork-Shiley prosthesis. Maximal encroachment was present in the vicinity of the lesser orifice. The prosthesis was also replaced at the same operation. Calcified, vascularized fragments of the aortic valve were received, together with the excised Bjork-Shiley prosthesis and multiple fragments of the host tissue overgrowth. The latter had the histological appearance of compacted fibrin and fibrous tissue. The cloth of the sewing ring of the prosthesis appeared to have been damaged during surgical removal.

(c) The third patient, (no clinical data available), had the disc of the Bjork-Shiley prosthesis totally immobilized by an overgrowth of host pannus tissue (see Figure 7.1).

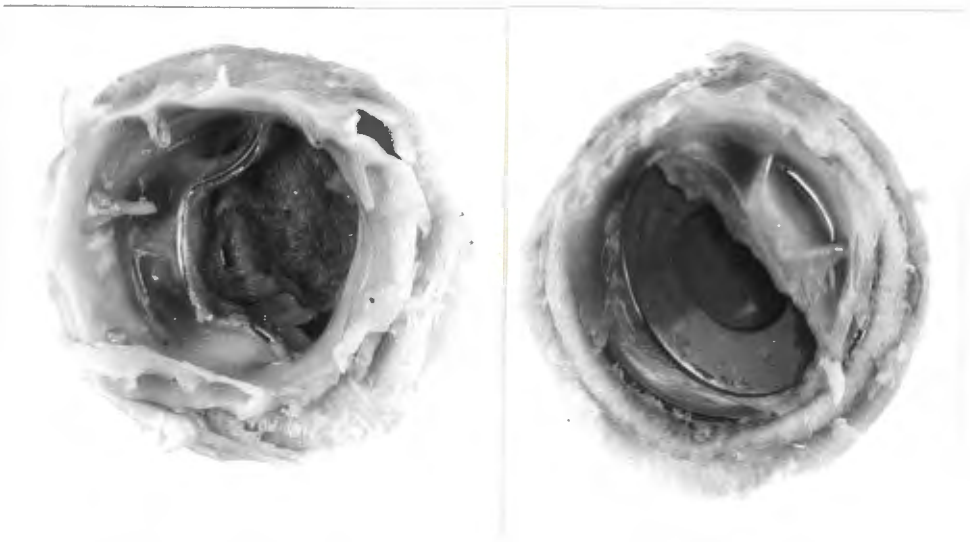


Figure 6.1 : Bjork-Shiley prosthesis is immobilized by an overgrowth of host tissue which has probably formed in response to thrombus deposited on the valve. Unorganized thrombus is seen on the undersurface of the disc (left-hand picture). Such immobilization will also favour further thrombosis on the prosthesis.

DOUBLE VALVE REPLACEMENT

Only a single patient was autopsied with Bjork-Shiley prostheses replacing both the mitral and tricuspid valves. The patient was a 44-year-old coloured female with chronic rheumatic heart disease and insulin-dependent diabetes mellitus. In addition to her mitral and tricuspid valvular disease, the patient had mild aortic stenosis and incompetence. The patient died 4 hours post-operatively due to a massive haemorrhage from numerous acute gastric erosions. No organ infarcts were noted at autopsy. An incidental colloid goitre of the thyroid gland was present. No heart weight was available, but both prosthetic valves were securely inserted.

Scanty fibrin thrombus was noted on the atrial aspect of the sewing ring of the tricupid prosthesis.

PRINCIPAL CAUSES OF DEATH IN 13(*) AUTOPSIED PATIENTS WITH BJORK-SHILEY VALVE PROSTHESES.

The principal causes of death were as follows : (a) due to error in pre-operative diagnosis, 2 ; (b) due to error in operative technique, 5 ; (c) due to problems inherent in the Bjork-Shiley valve, 1 ; (d) due to post-operative complications, 2 ; (e) unrelated to the cardiac operation, 2 ; (f) unknown causes, 1.

(* The death of the 14th patient, who did not survive re-operation, is attributable to calcific stenosis of the previous xenograft valve).

COMMENT

The Bjork-Shiley prosthesis has not been used very often as a valve substitute in our institution since no policy for its systemic use has been applied. The prosthesis has been used when batches of the valves have been provided for evaluation by the manufacturers or at times of transition between the formal use of other valve prostheses or in special circumstances where the use of other currently available valve prostheses was contraindicated e.g., heterograft valves in young persons, or in patients with narrow aortic roots.

The number of my autopsy patients with Bjork-Shiley valve prostheses is too small for any definite conclusions to be drawn regarding the frequency of fatal complications. One fact that does emerge is that systemic thromboembolism was not a prominent feature. None of the prostheses examined showed evidence of significant wear or variance. Errors in operative technique accounted for 39% of the deaths and valve-related problems were responsible for only 8% of the deaths.

Thromboembolic events are the most common and dreaded complication of cardiac valves(2) including the Bjork-Shiley(3-35), despite the neglible incidence of this complication in my small series of necropsy patients. Thrombosis of the Bjork-Shiley prosthetic cardiac valve may occur in any valve position and regardless of anticoagulant status(22). Review of cases reported in the literature suggests that the cumulative incidence of thrombosis of Bjork-Shiley prostheses is about 2% in the aortic position and about 4% in the mitral position. Prevention of this complication is dependent upon continuous anticoagulation with warfarin ; even temporary interruption or alteration of anticoagulation regimen may be detrimental. Although changes in anticoagulant therapy may rarely precipitate sudden thrombosis, in most cases a period averaging 10 months is

required for pannus of organized thrombus to build up enough to cause acute thrombosis and valve malfunction(22). Operation to remove the thrombus or to replace the prosthesis is usually needed for left-sided cardiac prostheses, but thrombosed valves in the tricuspid position may be successfully treated with fibrinolytic medical therapy. Peterffy et al.(18) suggest that red thrombus on Bjork-Shiley valves may be amenable to such therapy, which should not be prolonged for more than 24 hours and, if unsuccessful, the patient should undergo valve replacement. Others(5) stress that, as soon as obstruction of the prosthesis is recognized, the patient should undergo immediate surgery. Copans et al.(5) recommend that the Bjork-Shiley valve should only be used in the mitral area if excellent control of anticoagulation can be guaranteed.

Bjork and Henze(4) report an experience with 300 Bjork-Shiley aortic valvular implants and state that they encountered no cases of encapsulation or massive thrombosis in patients who were adequately anticoagulated. Two of their patients who developed massive thrombosis on their Bjork-Shiley aortic valves had received no anticoagulants. One patient underwent valve replacement and the other had operative removal of the thrombus only. This was facilitated by temporary removal of the disc. These authors stress that this method cannot be recommended for general use as an inexperienced surgeon may bend the struts so that the disc will not function properly after re-insertion. A decade later, Alvarez et al.(36) propose that thrombectomy should be the treatment of choice for a thrombosed Bjork-Shiley prosthesis, since no deaths in the literature have been attributed to the procedure. Moulton(37) questions whether thrombectomy is really a proven procedure.

Thrombosis has been a particular problem with Bjork-Shiley valves implanted in the tricuspid position(38) and in patients with multiple Bjork-Shiley prostheses(39). The latter study shows that the cumulative incidence of thrombosis in patients with multiple prostheses is 26.8% at six years.

Coumarin anticoagulation in pregnancy may result in foetal malformation and haemorrhagic complications(40). McLeod et al.(40) reported the case of a young woman who was given low dose heparin from the 17th week of pregnancy. Though there was a successful foetal outcome, heparin did not prevent thrombosis on the prosthesis and its continuation into the puerperium proved nearly fatal. Wong et al.(41) described a patient with a Bjork-Shiley aortic prosthesis who had received no anticoagulants for 28 months. Sudden, severe intravascular haemolysis developed as a result of thrombosis of her aortic prosthesis. Several papers discuss the early diagnosis of thrombosis of the Bjork-Shiley valve prosthesis(42-44).

Yoganathan et al.(45) report on their findings in recovered Bjork-Shiley aortic valve prostheses and in vitro measurements of velocities in the near vicinity of a normally functioning and a parially occluded Bjork-Shiley valve. The amounts of thrombus formation varied from nearly total thrombotic occlusion, similar to that shown by Bjork et al.(46) and Fernandez et al.(47), to a thin layer of thrombus. Yoganathan et al.(45) attributed the thrombus formation and tissue overgrowth to the stagnation zone and the low shear in the minor outflow region. A ring-shaped radiopaque marker was incorporated into the disc in 1977 to assist in diagnosing massive thrombosis of this type of prosthesis(46). Dale(48) found that the Bjork-Shiley and Lillehei-Kaster disc valves were equally thrombogenic and that the rate was not lower than that in patients with Starr-Edwards aortic ball-valves. As we shall see later below, others have noted a lower rate of prosthetic thrombi in the Bjork-Shiley valves compared to the Starr-Edwards ball-valves.

A large number of articles deal with the clinical and haemodynamic features of clinically implanted standard and convexo-concave models of the Bjork-Shiley tilting disc valve prosthesis(49-67). Other authors deal with specific problems e.g., immediate post-operative regurgitant malfunction of a Bjork-Shiley aortic valve due to interfering Teflon of a

ventricular septal defect repair(68) ; retrograde left ventricular catheterization in patients with a Bjork-Shiley aortic valve prosthesis(69,70) ; prosthetic dehiscence(71) ; haemolysis due to para-prosthetic regurgitation(72,73) or death due to complete prosthetic detachment(74). Koops and Puschel(75) describe a rare fatal complication in a patient who died of acute malfunction of her Bjork-Shiley aortic valve prosthesis caused by a large thromboembolus which originated in her left atrium. Silver(76) describes wear in Bjork-Shiley prostheses recovered at autopsy or at operation.

Strut fractures have occurred with the new type of concavo-convex Bjork-Shiley prosthesis which opens to 70 degrees(77) and 14 such fractures have occurred worldwide(78). The fractures have all occurred less than 14 months after valve implantation - most have been in the mitral position, but some were aortic implants. The basic problem is a fault in strut design(78) and the prosthesis has been withdrawn from the market. Strut fracture may have disastrous clinical consequences, but some patients have been saved by emergency valve replacement(79,80).

Obstruction of the Bjork-Shiley valve by chordal tissue(81), sutures(82-84), early post-operative pannus ingrowth(85), tissue detached from the aortic intima(86), and septal interference of mitral Bjork-Shiley prosthesis(83,87) have been documented. Echocardiography has been used to detect dehiscence(88) and thrombosis(23) of Bjork-Shiley prostheses. Verdel et al.(89) developed a method in which cineradiography is used for the assessment of the opening angle of implanted Bjork-Shiley valves.

Henze et al.(90) describe the cause of death and the main pathological findings in 20 patients following 161 Bjork-Shiley aortic valve implant operations. Myocardial failure (9 patients) was the predominant cause of death. The remainder died of cerebral haemorrhage (3 patients), malignancy (3 patients), infection (2 patients), dissecting aortic aneurysm (1 patient), hepato-renal syndrome (1

patient) and thromboembolism (1 patient). All 20 hearts showed gross cardiomegaly. Coronary perfusion during aortic valve replacement was considered to be of great importance in reducing the incidence of massive sub-endocardial myocardial necrosis.

Roberts and Hammer(91) describe the clinical and autopsy findings in 46 patients who had one or more cardiac valves replaced with Bjork-Shiley prostheses and compared the latter with the findings in patients with caged-ball, caged-disc, and trileaflet prostheses. The Bjork-Shiley valves gave less problems with regard to disproportion, haemolysis (as judged by renal haemosiderosis), and prosthetic thrombi. No instance of prosthetic wear or variance was noted over the relatively short 3 to 30 months (mean = 11) follow-up period. Forty percent of their early deaths (less than 2 months post-operation) were due to unknown causes, 18% were due to bleeding, coronary heart disease accounted for 15%, uncorrected associated valvular disease 12%, infection 9%, and prosthetic dysfunction was encountered in 6%. The latter figure is similar to the 8% incidence of valve-related deaths in my series. Principal causes of the 13 late deaths reported by these authors(91) was as follows (my percentages) : prosthetic valve endocarditis, 31% ; unknown, 23% ; prosthetic valve thrombosis,23% ; aortic regurgitation, 15% ; and coronary heart disease, 8%. A variety of clinical reports(92-102) indicate an overall similar experience to that discussed above. Roberts and Hammer(91) and others(103-105) caution that even mild aortic incompetence may cause cocking of the mitral disc of a caged disc prosthesis. Roberts and Hammer(91) further suggest that aortic incompetence may prevent proper opening of a mitral tilting disc prosthesis and lead to mitral prosthetic dysfunction, as was illustrated by one of their patients.

CHAPTER 7.

PATHOLOGY OF CARDIAC VALVE REPLACEMENT WITH THE LILLEHEI-KASTER PIVOTING-DISC VALVE PROSTHESIS

CHAPTER 7.

PATHOLOGY OF VALVE REPLACEMENT WITH THE LILLEHEI-KASTER PIVOTING-DISC CARDIAC VALVE PROSTHESIS

The yearly survival of patients after implantation of Lillehei-Kaster prostheses and the incidence of embolism events are listed in Tables 7.1 and 7.2. The actuarial survival rate at 5 years was 63.5% and 72.4% of patients were free of embolic events.

AORTIC VALVE REPLACEMENT

Nine patients with Lillehei-Kaster aortic valve prostheses were autopsied ; there were 4 whites, 4 coloureds and one black patient. Five of the 9 patients were females and the 9 patients had a mean age of 43.3 years (S.D.= 16.4). The mean postoperative survival period of the whole group was 366.8 (S.D.= 596.7) days with a range of from 1 to 1800 days. The nature of the native aortic valvular disease leading to aortic valve replacement with Lillehei-Kaster aortic valve prostheses in the 9 patients was as follows : chronic rheumatic-type deformity 3, aortic ring distortion due to an aortic dissecting aneurysm 1, senile tricuspid calcific aortic stenosis 1, calcified congenital bicuspid aortic valve 2, and other congenital anomalies of the aortic valve 2. The mean heart weight of these 9 patients was 555 grams (S.D.= 83). The principal causes of death (one each per patient) are indicated in Table 7.3. Table 7.4 lists other less important complications.

GROUP 1

Regarding the principal causes of death, errors in operative technique led to the deaths of 2 patients. In one there was obstruction of a small right coronary arterial ostium by the sewing ring of the prosthesis ; a patient with a pacemaker had unrecognized ventricular fibrillation during anaesthesia leading to irreversible anoxic cerebral damage. No cause of death was found in one patient (? arrythmia) and one had fatal myocardial failure. Lesser complications encountered included chest wound infection, and complete heart block due

TABLE 7.1 : YEARLY SURVIVAL AFTER IMPLANTATION OF LILLEHEI-KASTER PROSTHESES (1976 - 1982)

YRS. AFTER OP.	LIVE PTS.	EVENTS	DEATHS	SURVIVE INCOMPLETE INTERVAL	REMOVED FOR NEW OP.	INTERVAL SURVIVAL PROPOR.	CUMUL. SURVIVAL RATE
0-1/12	153	0	13	0	4	0.914	0.914
1/12-1	135	0	19	2	4	0.856	0.782
1-2	110	0	6	4	3	0.944	0.738
2-3	97	0	2	3	2	0.979	0.723
3-4	90	0	1	1	5	0.989	0.715
4-5	83	0	9	2	3	0.888	0.635
5-6	69	0	4	1	3	0.940	0.597
6-7	61	0	0	3	2	1.000	0.597

TABLE 7.2 : EMBOLISM EVENTS AFTER IMPLANTATION OF LILLEHEI-KASTER PROSTHESES (1976 - 1982)

YRS. AFTER OP.	EVENT-FREE PTS.	EVENTS IN INTERVAL	EVENT-FREE DEATHS	SURVIVE INCOMPLETE INTERVAL	REMOVED FOR NEW OP.	INTERVAL SURVIVAL PROPOR.	CUMUL. EVENT-FREE RATE
0-1/12	132	2	13	0	4	0.984	0.984
1/12-1	112	5	13	0	2	0.952	0.937
1-2	92	5	4	1	0	0.944	0.885
2-3	82	3	1	0	1	0.963	0.852
3-4	77	5	0	1	2	0.934	0.796
4-5	69	6	4	0	2	0.909	0.724
5-6	57	2	4	0	2	0.963	0.697
6-7	49	2	0	1	2	0.958	0.668

TABLE 7.3 : PRINCIPAL CAUSES OF DEATH IN 9 PATIENTS WITH LILLEHEI-KASTER AORTIC VALVE PROSTHESES

GROUP 1	
ANAESTHETIC MISHAP	1
OPERATIVE TECHNIQUE ERROR	1
MYOCARDIAL FAILURE	1
UNKNOWN CAUSE	1
GROUP 2	
ERROR PRE-OPERATIVE DIAGNOSIS	1
OPERATIVE ERROR	1
THROMBOSED PROSTHESIS	1
INFECTED PROSTHESIS	1
CORONARY THROMBOSIS	1

TABLE 7.4 : NON-FATAL COMPLICATIONS/ASSOCIATED CONDITIONS IN 9 PATIENTS WITH LILLEHEI-KASTER AORTIC VALVE PROSTHESES

GROUP 1	
SUTURES NEXT TO SINO-ATRIAL NODE	1
INFECTED CHEST WOUND	1
COMPLETE HEART BLOCK	1
SEVERE CORONARY ATHEROSCLEROSIS	1
GROUP 2	
AORTIC DISSECTION	1
SEVERE CORONARY ATHEROSCLEROSIS	2
MID-ZONAL LIVER NECROSIS	1
ANTICOAGULANT EXCESS BLEEDING	1

to calcification of the central fibrous body. Infarcts were most commonly encountered in the heart (2 cases), brain (2 cases) and kidneys (2 cases), spleen (1 case) and bowel (1 case). One patient had greater than 75% narrowing of the major coronary arteries.

Two of the 4 patients had bland thrombus on their Lillehei-Kaster prosthesis. In both the thrombus involved the sewing ring and extended variably into the lesser orifice of the prosthesis. Proliferative phase Aschoff bodies were noted in the heart of one of the 4 patients.

GROUP 2

The 5 group 2 patients died of the following causes (see Table 7.3) : error in pre-operative diagnosis (unrecognized subaortic stenosis) ; operative trauma led to bowel perforation which was followed by infective pericarditis and a mediastinitis ; thrombosed prosthesis ; infective endocarditis ; and myocardial infarction due to coronary thrombosis. The patient with the thrombosed prosthesis had received no anticoagulants.

Lesser complications included ischaemic heart disease in 2 patients (greater than 75% narrowing of one or more of the major coronary arteries), a dissecting aneurysm, and mid-zonal liver necrosis of unknown cause and a subdural haematoma due to bleeding induced by excessive anticoagulant therapy. Infarcts were noted in the kidneys of 2 different patients, in the hearts of 3 and in the brains of 2 cases as well as the lungs of another patient. Two out of the 5 patients had bland thrombus on their Lillehei prosthesis. This filled the lesser orifice of one valve and totally immobilised the other prosthesis. A patient with infected vegetations on the prosthesis had pyaemic abscesses in the kidneys and myocardium.

PRINCIPAL CAUSES OF DEATH AND COMMENT

Four out of the 9 patients died due to either an error in pre-operative diagnosis or due to errors in operative technique. Thrombosis, when present, favoured the lesser orifice of the prosthesis.

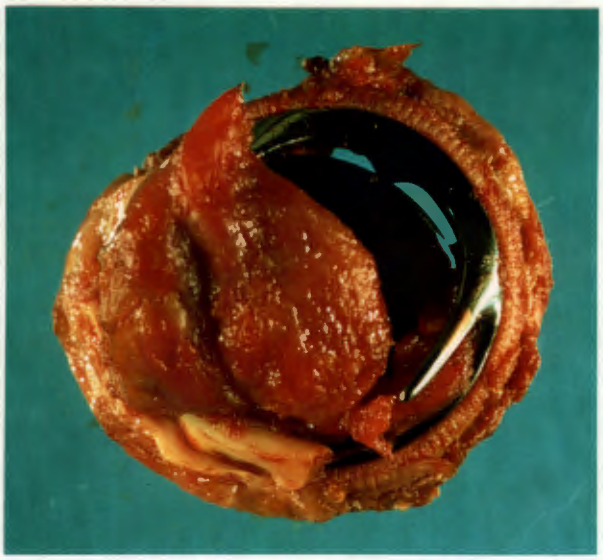


Figure 7.1 : Massive thrombus in lesser orifice has led to immobilization of this Lillehei-Kaster mitral valve prosthesis.

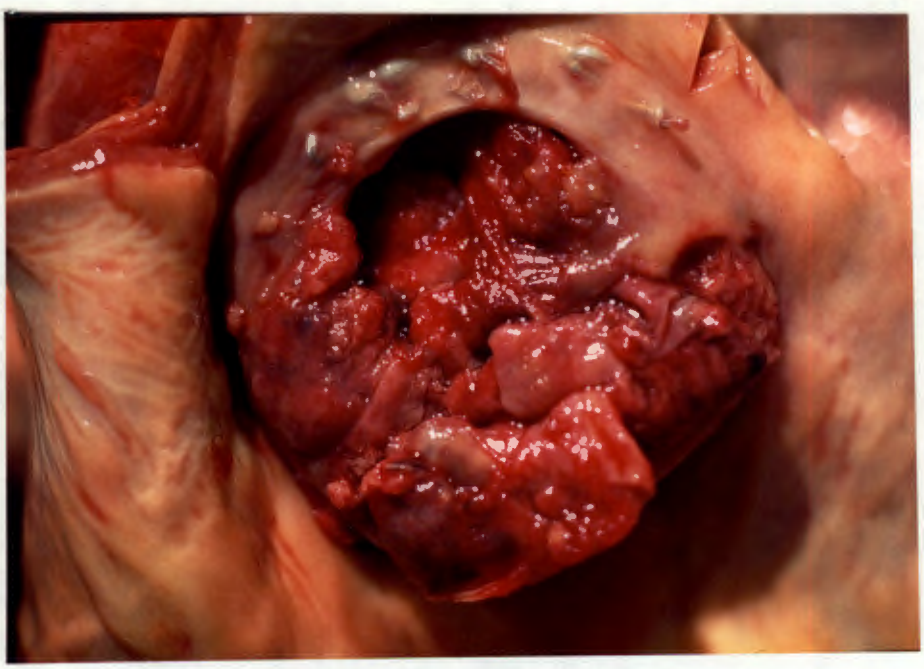


Figure 7.2 : Infected Lillehei-Kaster prosthesis 210 days after implantation. Staphylococcus albus was cultured from the blood during life and from the obstructive vegetations at autopsy.

MITRAL VALVE REPLACEMENT

Seven patients with Lillehei-Kaster mitral valve prostheses were autopsied. There were 4 blacks, 2 whites and 1 coloured patient. Their mean age was 27.4 years (S.D.= 15.2) and the range was from 18-59 years. All seven patients underwent heart valve replacement for post-rheumatic mixed mitral valve disease. The mean post-operative survival was 453 days (S.D.= 552) with a range of 4-1350 days. Two patients survived 7 days or less and the other 5 survived 38 days or longer post-operatively. The mean heart weight was 577 grams (S.D.=139) and the range was 450-808 grams.

Principal causes of death (one per patient) are given in Table 7.5 and lesser complications are listed in Table 7.6. No patients died due to an error in pre-operative diagnosis or due to error in operative technique. Three patients died because of problems with the prosthetic valve (Figs. 7.1 and 7.2) and another 2 died of post-operative complications unique to open-heart surgery. No morphological cause of death was noted in 2 patients. Lesser complications (Table 7.6) included cardiac catheterization-induced dissecting aneurysm of the aorta in one patient and massive thrombosis on the atrial suture line in another patient. Lung and spleen were the organs with the most infarcts. No data regarding organ infarcts were available in 2 of the seven patients since the hearts only were referred for examination.

Thrombus was noted on two of the Lillehei-Kaster mitral valve prostheses. In both instances abundant thrombus filled the lesser orifice and led to almost total immobilization of the prosthesis. Scantier thrombus was present on both aspects of the sewing ring and within the greater orifice. Aschoff bodies were seen histologically in 2 out of the 7 hearts.

TABLE 7.5 : PRINCIPAL CAUSES OF DEATH IN 7 PATIENTS WITH LILLEHEI-KASTER MITRAL VALVE PROSTHESES

UNKNOWN	2
ANTICOAGULANT EXCESS BLEEDING	2
THROMBOSED PROSTHESIS	2
INFECTED PROSTHESIS	1

TABLE 7.6 : NON-FATAL COMPLICATIONS/ASSOCIATED CONDITIONS IN 7 PATIENTS WITH LILLEHEI-KASTER MITRAL VALVE PROSTHESES

CATHETER-INDUCED AORTIC DISSECTION	1
MASSIVE ATRIAL SUTURE LINE THROMBUS	1
SUBARACHNOID HAEMORRHAGE	1
THROMBOEMBOLUS S-A NODE ARTERY	1

ORGAN INFARCTS:

LUNG	2
SPLEEN	2
KIDNEYS	1
HEART	1
BRAIN	1

DOUBLE VALVE REPLACEMENT WITH THE LILLEHEI-KASTER PROSTHESIS

Two patients came to autopsy with Lillehei-Kaster prostheses in both the aortic and mitral positions. The first patient, a 39-year-old black female, was operated upon as an emergency because of acute aortic incompetence due to infective endocarditis. The patient had only received antibiotics for 3 days pre-operatively. A tricuspid annuloplasty was also performed. Death occurred 210 days post-operatively due to progressively worsening myocardial failure. The heart, which weighed 523 grams, showed focal myocarditis. Both Lillehei prostheses bore abundant antemortem thrombi on the sewing ring and 'horns' of the prosthesis, but there was no histological evidence of infection. Thrombus was more plentiful on the mitral prosthesis. No organ infarcts were detected, but acute gastric erosions were seen.

The second patient, a 15-year-old black female with chronic rheumatic heart disease, died of cardiac failure 6.5 months after cardiac surgery. Immediately prior to death her serum potassium had been abnormally elevated. Both aspects of the Lillehei mitral prosthesis were covered by large amounts of antemortem thrombus,which was also continuous with left atrial thrombi. These combined thrombi, which appeared to be of several weeks duration, produced severe orificial obstruction of the mitral prosthesis. Scanty antemortem thrombus was detected on the inferior aspect of the Lillehei aortic valve prosthesis. A small pulmonary infarct was also present, together with evidence of a rheumatic pneumonitis. The heart weighed 690 grams and numerous Aschoff bodies were seen histologically.

PRINCIPAL CAUSES OF DEATH IN PATIENTS WITH MITRAL AND DOUBLE VALVE REPLACEMENT

Five out of the 7 patients' deaths were due to problems directly related to the Lillehei-Kaster mitral valve prosthesis itself.

COMMENT

Lillehei and Kaster(1,2) introduced the concept of a pivoting disc prosthetic valve in an attempt to improve on the haemodynamic performance of the caged-ball prosthetic valves. The present studied has shown that prosthesis-related principal causes of death were more commonly encountered in patients with mitral valve prostheses and in group 2 patients with Lillehei-Kaster aortic valve prostheses. Myocardial failure may have favoured the development of thrombi on some of the valvular prostheses. Conversely, thrombosis upon the prosthesis may have produced sufficient obstruction in some cases to account for the cardiac failure. Non-infected thrombus on the Lillehei-Kaster prosthesis was primarily situated within and around the lesser orifice of the valve. My patient with massive left atrial suture line thrombus is similar to the cases decribed by Ben-Shachar et al.(3), in which the mural thrombi were attributed to operative trauma. Such thrombus may also be a source of late post-operative thromboembolism.

Gibson et al.(4) have delineated the phonocardiographic and echocardiographic characteristics of the Lillehei-Kaster eccentric monocusp central flow valve prosthesis. Clinical and haemodynamic assessments of the valve have also been published(4-16). Rao et al.(17) compared the incidence of chronic haemolysis following mitral valve replacement with the Lillehei-Kaster valve and with some other cardiac valvular prostheses. In isolated mitral valve replacement 66% showed

compensated haemolysis compared to 42% in Bjork-Shiley valves, 85% in composite seat Starr-Edwards valves and none in frame-mounted homograft valves. Poppet jamming of a Lillehei-Kaster prosthesis due to impaction of a left atrial monitoring line during mitral valve replacement has been described(18). Behle and Brown(19) described a case with late snaring of a Lillehei-Kaster prosthesis by a fragment of left atrial monitoring catheter. The catheter had snapped at its point of fixation and the retained fragment caused immobilization of the disc. Jamming of a disc prosthesis may thus be due to factors other than thrombosis or entrapped sutures.

Nitter-Hauge(4) reported favourable results after a relatively short follow-up period of 1 year in 68 patients with single aortic valve replacement with either a Lillehei-Kaster pivoting disc valve or a Bjork-Shiley tilting disc valve. Lillehei-Kaster valves implanted in the mitral position(6) gave similarly good results after 12 to 24 months follow-up and compared well with the Bjork-Shiley prosthetic valve(7). Intra-operative haemodynamic evaluation of the Lillehei-Kaster valve by Starek et al.(8) showed it to have improved haemodynamics compared to the various models of caged-ball valves. In vivo evaluation of the Lillehei-Kaster valve by Sigwart et al.(9) showed that the maximum opening angle of 80 degrees was never reached in this group of patients ; opening angles ranged from 57 to 74 degrees without evidence of disc malfunction. They concluded that incomplete opening of the disc occluder is not necessarily a sign of disc malfunction, since there was no correlation between the ratio of effective to geometric valve area.

Starek et al.(10) reported on the clinical evaluation of 133 patients with Lillehei-Kaster valves who had been followed for 4 years. Patients with aortic valve replacement had remained free of valve-related problems. Patients with mitral valve implants had a 10% incidence of valve thrombosis, which was attributed to inadequate anticoagulation or to the use of

an inappropriate suturing technique, or both. In a discussion appended to the same paper(10), Lillehei warned against inserting too large a Lillehei-Kaster prosthesis in the mitral area ; the danger being that a small left ventricle may lead to one of the struts becoming embedded in the mural myocardium. This may provoke scar tissue growth that may slowly impede disc motion.

From Durban, South Africa , Mitha et al.(11) reported a disturbing incidence of thrombosis in their patients with Lillehei-Kaster valves involving at least 10% of the mitral implants and 5% of the aortic, which led them in 1974 to stop using the prosthesis. They attributed the thrombosis to late prosthetic disproportion following shrinkage in size of the heart post-operatively. Minimal impingement and cocking of the disc on the ventricular endocardium results in thrombosis of the prosthesis and of the left atrium. Mitha et al.(11) postulate that insertion of smaller mitral prostheses may have obviated the thrombotic complications. Roberts et al.(20) drew attention to the fact that the regurgitant jet of blood of unsuspected severe aortic incompetence may interfere with the opening of disc valves. Forman et al.(12) from our institution catheterized 26 patients with Lillehei-Kaster valves and showed no advantage over other types of prosthetic valves. Dale(13) reported that arterial thromboembolic complications are a considerable problem with both the Lillehei-Kaster and Bjork-Shiley disc valves, including those in the aortic position. Zwart(14) found an incidence of thromboembolism of 5.0 per 100 patient-years and the actuarial survival was 81% at 5 years with the Lillehei-Kaster prosthesis. Christo et al.(15) found that thrombosis was an important late complication of heart valve replacement with this prosthesis. Uhrenholdt et al.(16) discussed the cardiac catheterization findings in patients after insertion of a Lillehei-Kaster prosthesis and explained how to distinguish clinically between myocardial failure and valve dysfunction.

Despite the adequate number of clinical reports on the

Lillehei-Kaster valve prosthesis, I am not aware of any report that specifically addresses the pathology associated with the implantation of this prosthesis. Roberts et al.(20) have reported the pathology of 61 autopsied patients with a discoid prosthesis of the Hufnagel type. The latter type of prosthesis was found not to be an ideal substitute cardiac valve. It thromboses despite adequate anticoagulant therapy, it is intrinsically stenotic, the disc degenerates and it haemolyses erythrocytes.

CHAPTER 8.

PATHOLOGY OF CARDIAC VALVE REPLACEMENT WITH THE St JUDE MEDICAL VALVE PROSTHESIS

CHAPTER 8.

PATHOLOGY OF CARDIAC VALVE REPLACEMENT WITH THE St JUDE MEDICAL VALVE PROSTHESIS

Stevens(1) from our institution reported that in a 40 month period (February 1979 to August 1981) 333 patients received 399 St Jude Medical (SJM) valves (118 aortic, 149 mitral, 59 aortic and mitral, 3 tricuspid plus mitral, 2 tricuspid, mitral and aortic, and 2 isolated tricuspid). The age range was 1.5 to 75 years (mean 34). There were 177 males and 156 females (181 coloured, 87 white,and 65 black patients). The operative mortality was 4.8% and 306 patients were followed from 1 to 39 months (mean 15.4). Seventeen valve failures occurred : 13 obstructed acutely, 3 had haemolysis immediately post-operatively and 1 had a late para-valvular leak needing re-operation. Of the 13 obstructed valves, 7 had emergency re-operation with 1 death. Five died suddenly in pulmonary oedema, and 1 had echocardiographic and aucultatory evidence of an obstructed tricuspid valve. None of these patients was on anticoagulants. Fifty embolic events occurred in 42 patients within the first 30 days, and 26 when anticoagulation was unsatisfactory. Seventeen patients had severe anticoagulant-induced bleeding. Re-study of 33 patients showed small mean gradients across the SJM prostheses (mitral 0-6 mm Hg, aortic 0-26 mm Hg). Stevens(1) concluded that the SJM valve has good haemodynamics, a low incidence of emboli, but the sudden thrombosis of the valve in the non-anticoagulated patients stresses the need for anticoagulant therapy.

Tables 8.1 and 8.2 give the yearly survival and embolism events respectively in patients with SJM prosthetic heart valves at Groote Schuur Hospital for the years 1976 to 1982 inclusive.

TABLE 8.1 : YEARLY SURVIVAL AFTER IMPLANTATION OF St. JUDE MEDICAL PROSTHESES (1976 - 1982)

YRS. AFTER OP.	LIVE PTS.	EVENTS	DEATHS	SURVIVE INCOMPLETE INTERVAL	REMOVED FOR NEW OP.	INTERVAL SURVIVAL PROPOR.	CUMUL. SURVIVAL RATE
0-1/12	551	0	26	0	5	0.953	0.953
1/12-1	473	0	15	120	10	0.963	0.918
1-2	328	0	9	119	4	0.966	0.887
2-3	196	0	8	119	1	0.941	0.835
3-4	68	0	2	54	1	0.951	0.794
4-5	11	0	0	11	0	1.000	0.794
5-6	0	0	0	0	0	1.000	0.794
6-7	0	0	0	0	0	1.000	0.794

TABLE 8.2 : EMBOLISM EVENTS AFTER IMPLANTATION OF St. JUDE MEDICAL PROSTHESES (1976 - 1982)

YRS. AFTER OP.	EVENT-FREE PTS.	EVENTS IN INTERVAL	EVENT-FREE DEATHS	SURVIVE INCOMPLETE INTERVAL	REMOVED FOR NEW OP.	INTERVAL SURVIVAL PROPOR.	CUMUL. EVENT-FREE RATE
0-1/12	537	4	25	0	5	0.992	0.992
1/12-1	456	26	12	111	8	0.933	0.926
1-2	299	12	2	108	3	0.951	0.881
2-3	174	6	3	107	0	0.950	0.837
3-4	58	1	0	48	0	0.971	0.813
4-5	9	0	0	9	0	1.000	0.813
5-6	0	0	0	0	0	1.000	0.813
6-7	0	0	0	0	0	1.000	0.813

St JUDE MEDICAL AORTIC VALVE PROSTHESIS

Ten patients with St Jude medical prostheses replacing the aortic valve were autopsied. There were 6 males and 4 females, and 3 whites, 5 coloureds and 2 blacks. The pre-operative native aortic valvular diseases were as follows : syphilitic aortitis 2, chronic rheumatic heart disease 3, infective endocarditis 1, aortic nodular sclerosis 1, calcified bicuspid aortic valve 2 and unknown 1.

GROUP 1

Seven patients who died less than 30 days post-operatively had a mean age of 47.4 years (S.D.= 18) with a range of 19-66 years. The mean post-operative survival period was 9.5 days (S.D.= 9.9) with a range of from 17 hours to 25 days. The mean heart weight was 773 grams (S.D.=250), and the range was from 466 to 1065 grams. Only one of the 7 prostheses showed scanty antemortem thrombi on the sewing ring ; all of the other prostheses appeared normal in this regard. One heart,which was referred for examination from my forensic colleagues, contained a St Jude prosthesis in which one of the pyrolytic carbon leaflets had been broken into two fragments. One fragment remained in situ within the prosthesis, whilst the other lay free within the left ventricle. The problem was to decide whether the fragmentation had occurred during life or if it was artefactual in nature. There was a scratch mark at the edge of the fractured leaflet and the forensic pathologist who had performed the original autopsy later recollected that he had opened the left ventricle with a large pair of scissors and had inadvertently tried to cut across the prosthesis. The pyrolytic carbon discs of this prosthesis are evidently rather brittle.

The 7 patients showed infarcts in the following organs : brain (bilateral) 1, and left ventricle 1. It should be noted that in 4 of the 7 patients, only the heart was received for examination and few details were available regarding the

general autopsy findings. In addition, the patient with the bilateral cerebral infarcts had developed one of these infarcts pre-operatively due to infective endocarditis. The myocardial infarct listed above was due to coronary atherosclerosis. This patient plus another had saphenous vein coronary arterial bypass grafts inserted at the time of the valve surgery. The principal causes of death in the group 1 patients are indicated in Table 8.3. A Klebsiella species was cultured at postmortem from the one patient's infected pulmonary infarcts. Associated conditions in group 1 included a small pulmonary embolus in 1 patient, and hereditary spherocytosis in another. A third patient had systemic hypertension, atheromatous emboli in small renal arteries and haemorrhages in the atrioventricular node and bundle of His.

TABLE 8.3 : PRINCIPAL CAUSES OF DEATH (1 PER PATIENT) IN 10 PATIENTS WITH St JUDE MEDICAL AORTIC VALVE PROSTHESES

GROUP 1	
UNKNOWN	3
BLEEDING (HAEMATOLOGICAL ABNORMALITY)	1
MYOCARDIAL FAILURE	1
RUPTURED MYCOTIC ANEURYSM (PRESENT PRE-OPERATIVELY)	1
INFECTED PULMONARY INFARCTS (PRESENT PRE-OPERATIVELY)	1
GROUP 2	
INFECTIVE ENDOCARDITIS	3

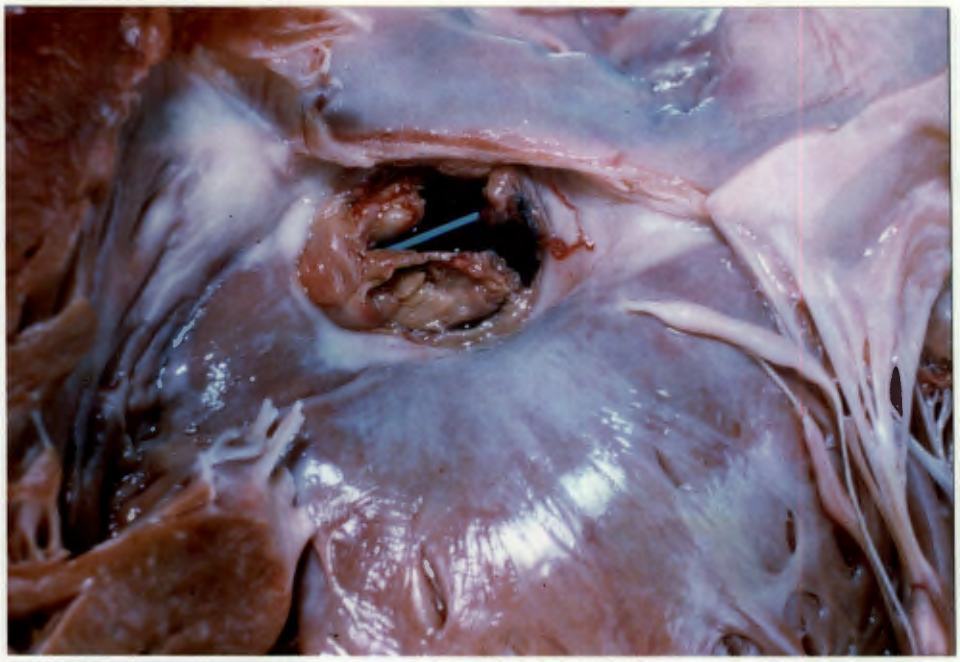


Figure 8.1 : Infected (Staphylococcus albus) St Jude Medical aortic valve prosthesis viewed from the left ventricle.

GROUP 2

The 3 patients who survived longer than one month post-operatively (Table 8.3) were two coloured woman aged 67 and 71 years and a 33 year old black woman. Post-operative survival had been 32, 120 and 42 days respectively. Heart weights were 563, 650 and 370 grams. All three patients died of infective endocarditis (Fig. 8.1). Pre-disposing factors for infection were the presence (1 each) of the following diseases in these 3 patients : diverticulitis, septic abortion with infective endocarditis pre-operatively, and post-operative wound infection. The bacteria inculpated in these 3 patients with infected prostheses consisted of Staphylococcus aureus, Pseudomonas and coliforms. Two patients had ring abscesses and the patient with the Staphylococcal infection had two mycotic aneurysms in the aortic root. Associated conditions observed in the 3 patients included

bronchopneumonia 1, gallstones 1, subarachnoid haemorrhage 1, and focal segmental glomerulonephritis 1. Only one of the 3 patients showed signs of embolism (to the hand, leg and heart).

MITRAL VALVE REPLACEMENT

Nine patients with St Jude prostheses in the mitral position were autopsied. The native mitral valvular diseases leading to operation were as follows : chronic rheumatic heart disease 5, congenital mitral valve disease 2 (parachute mitral valve ; ostium primum defect with cleft mitral valve), floppy mitral valve 1 and unknown 1.

GROUP 1

The 6 patients who died less than 30 days post-operatively had a mean age of 23.5 years (S.D.= 18.2) and a range of 6 to 59 years. There were 3 coloureds, 2 blacks and 1 white patient. Four of the 6 subjects were females. The mean post-operative survival period was 7.7 days (S.D.= 10.2) with a range of 36 hours to 28 days. The mean heart weight was 468 grams (S.D.= 134) with a range of 232-610 grams. Scanty thrombi were present on the left atrial (inflow) aspect of the sewing ring in 2 out of the 6 prostheses. These 6 patients showed the following organ infarcts : spleen 1, kidney 1, pituitary 1. Table 8.4 gives the principal cause of death for each of the 6 patients. Non-fatal complications/associated conditions included the following : (i) dehiscence of the prosthesis from the patch used to close an ostium primum defect. This may possibly have been artefactually produced by pre-terminal external cardiac massage. (ii) Subarachnoid haemorrhage, (iii) Takayasu's aortitis and acute renal tubular necrosis, and (iv) shock lung.

TABLE 8.4 : PRINCIPAL CAUSE OF DEATH (1 PER PATIENT) IN 9 PATIENTS WITH St JUDE MEDICAL MITRAL VALVE PROSTHESES

GROUP 1	
UNKNOWN	4
ANTICOAGULANT EXCESS,BLEEDING	1
PARA-PROSTHETIC LEAK	1
GROUP 2	
ANTICOAGULANT EXCESS,BLEEDING	1
MYOCARDIAL FAILURE	1
PNEUMONIA	1

GROUP 2

Three patients (a 50-year-old coloured female, a 56-year-old white female and an 18-year-old black female) died more than 30 days post-operatively. Post-operative survival was 38, 59 and 180 days respectively. The respective heart weights were 462, 593 and 400 grams. Principal causes of death are indicated in Table 8.4. The patient who died of myocardial failure showed very extensive thrombus lining most of the left atrium, as well as upon both aspects of the St Jude mitral valve prosthesis and the septal and inferior walls of the left ventricle. The primary abnormality is interpreted to be the myocardial failure with the formation of stasis thrombi at these sites, rather than primary thrombotic occlusion of the St Jude prosthesis.

AORTIC AND MITRAL VALVE REPLACEMENT WITH St JUDE MEDICAL PROSTHESES

Autopsies were performed upon 8 patients with St Jude Medical prostheses in both the aortic and the mitral positions. Five of the 8 patients were females. There were 3 blacks and 4 coloureds. The aetiology of the native heart valvular diseases leading to double valve replacement were as follows : chronic rheumatic heart disease 5, floppy mitral valve with superimposed infective endocarditis 1 and unknown 2.

GROUP 1

The five patients who died early post-operatively had a mean age of 29.3 years (S.D.= 14.3) with a range of 15-46 years. Mean post-operative survival was 15 days (S.D.= 13) with a range of 20 hours to 30 days. The heart weights ranged from 298 grams (in a 15-year-old) to 644 grams, with a mean of 505 grams (S.D.= 135). All 5 St Jude mitral valve prostheses were free of thrombi, but one out of the 5 St Jude aortic prostheses bore infected vegetations. The 5 patients showed the following organ infarcts : brain 3, heart 2, kidney 2, spleen 2 and limbs 2. It should be noted that in one patient with infarcts of the brain, heart, spleen and kidney, the infarcts were old and appeared to antedate the double valve replacement operation. Table 8.5 lists the principal cause of death in these patients. Non-fatal complications/associated conditions observed in group 1 included a pulmonary primary tuberculous complex, an erroneous surgically created communication between the left ventricle and the right atrium sealed by a suture in the right atrium 1, acute renal tubular necrosis 1, disseminated intravascular coagulopathy 1 and pump lung 1.

TABLE 8.5 : PRINCIPAL CAUSES OF DEATH (1 PER PATIENT) IN 8 PATIENTS WITH St JUDE MEDICAL PROSTHESES IN THE AORTIC AND MITRAL POSITIONS

GROUP 1	
BLEEDING	1
AIR EMBOLISM	1
HEPATITIS	1
SEPTICAEMIA	1
INFECTIVE ENDOCARDITIS	1
GROUP 2	
THROMBOSED MITRAL PROSTHESIS	2
ANTICOAGULANT EXCESS,BLEEDING	1

GROUP 2

The three patients who died more than 30 days post-operatively were aged 30, 34 and 28 years. Two of the 3 were females, and all 3 were coloureds who had been operated upon for chronic rheumatic valvular heart disease. Only one out of the 3 heart weights was available (452 grams). Two of the 3 mitral valve prostheses in this group of patients were immobilized by thrombosis on both aspects of the prosthesis. The third patient had a low prothrombin index (13%) and bled spontaneously into her brain and vulva. The principal causes of death of these 3 patients are also included in Table 8.5. Both patients who died of thrombosed prostheses had inadequate anticoagulant control. One of these patients had attended the Casualty Department of Groote Schuur Hospital several times pre-terminally and had been reassured and sent home without seeing a cardiologist. She was finally admitted to hospital and did not survive re-operation. All of the deaths in this

group were attributable to problems inherent in the design and structure of the St Jude prosthesis.

St JUDE MEDICAL PROSTHETIC VALVE REPLACEMENT OF THE MITRAL AND TRICUSPID VALVES

Only one autopsy patient fell into this category. She was a 16-year-old black female with Marfan's syndrome and incompetence of both the mitral and tricuspid valves. Both valves were replaced by St Jude Medical prosthetic heart valves. At the time of the initial surgery the right upper pulmonary vein was inadvertently damaged and repaired. Two weeks post-operatively the patient the underwent re-operation because of severe thrombotic obstruction of the St Jude valve in the tricuspid position. The previously surgically repaired right upper pulmonary vein was totally occluded by thrombus. The patient did not survive the re-operation. Both ventricles showed myocytolysis, but no Aschoff bodies were seen. The left anterior descending coronary artery contained some calcified material, which appeared to be embolic in origin. The only infarct encountered was that seen in the lung.

TRICUSPID VALVE REPLACEMENT WITH A St JUDE MEDICAL VALVULAR PROSTHESIS

One patient, an 18-month-old white female, underwent isolated tricuspid valve replacement with a St Jude prosthesis due to severe tricuspid valve incompetence, which followed an episode of infective endocarditis. She also had had a previous exomphalos repaired. Sudden death occurred on the second post-operative day. Autopsy revealed an hypertrophied and fibrosed right ventricle and evidence of severe thromboembolic pulmonary hypertension. The St Jude prosthesis appeared

normal. Death was attributed to the severe pulmonary hypertension.

ASSOCIATED NON-FATAL CONDITIONS IN PATIENTS WITH St JUDE MEDICAL PROSTHESES

Non-fatal, associated conditions are listed in Table 8.6.

TABLE 8.6 : ASSOCIATED NON-FATAL COMPLICATIONS IN PATIENTS WITH St JUDE MEDICAL CARDIAC PROSTHESES

AORTIC VALVE REPLACEMENT	
LUETIC CORONARY OSTIAL STENOSIS	1
SPHEROCYTOSIS	1
GALLSTONES	1
SEVERE CORONARY ATHEROSCLEROSIS	2
SEPTIC ABORTION	1
GLOMERULONEPHRITIS	1
WOUND INFECTION	1
AORTIC & MITRAL VALVE REPLACEMENT	
TUBERCULOSIS	1
PUMP LUNG	1
RENAL TUBULAR NECROSIS	1
VULVAL HAEMATOMA	1
MITRAL VALVE REPLACEMENT	
SUBARACHNOID HAEMORRHAGE	1
MEDIASTINAL HAEMATOMA	1
SHOCK LUNG	1
TAKAYASU'S ARTERITIS	1
RENAL TUBULAR NECROSIS	1
MULTIPLE SUBDURAL HAEMATOMAS	1

SUMMARY OF PRINCIPAL CAUSES OF DEATH IN 29 PATIENTS WITH St JUDE MEDICAL VALVES

There were no deaths due to an error in pre-operative diagnosis. Three patients died due to an error in operative technique and the deaths of 9 were due to problems directly related to the St Jude Medical valve. Six patients died of post-operative complications, 4 died of complications unrelated to the cardiac operation and the causes of death were unknown in 7 patients.

COMMENT

The St Jude Medical (SJM) prosthetic heart valve is a rigid, bi-leaflet, central orifice, all pyrolytic carbon device that has gained widespread acceptance since its clinical introduction in 1977(2-5). Lillehei(6,7) has summarized the worldwide experience regarding the clinical and haemodynamic results with the SJM prosthetic valve. The prosthesis is being evaluated in 4 primary centres in the United States of America and by 13 other centres worldwide, including our institution. In vitro haemodynamic studies(8-11) show that, in general, the SJM valve represents a clear improvement in valve design with a low level of stenosis and a low regurgitant fraction. Catheterization data after SJM implantations in patients, including a report from our institution(12), were also favourable and the SJM haemodynamics are claimed to be superior to those reported for any other valve. Colman et al.(13) stated that the SJM valve is the prosthesis of choice over a bioprosthesis for mitral valve replacement under the following conditions : (a) a small valve ring, i.e. all that would accept only a prosthesis below 27 mm diameter ; (b) elevated left ventricular end-diastolic pressure ,including all forms of cardiomyopathies -

primary/secondary (ischaemic or rheumatic) ; or (c) giant left atrium. Gray and colleagues(14-16) and Dalichau et al.(17) came to similar conclusions. Kinsley(11) inserted a SJM aortic valve obliquely in 6 patients as a simple method for aortic root enhancement.

Starek et al.(18) found in vitro that the SJM valve was less vulnerable to leaflet entrapment than other mechanical valves e.g., the Lillehei-Kaster, Bjork-Shiley, Omniscience or Hall-Kaster disc valves. Whilst the disc of the latter 4 types of valves can be totally immobilised by a single interference anywhere around their circumference, the SJM valve proved to be vulnerable only at the areas immediately adjacent to the two pivot guards. Salvatore et al.(19) reported a case wherein a chordal remnant had immobilised one leaflet of a SJM mitral valve prosthesis in a closed position and the patient was in no distress. When fully open to 85 degrees, the large effective orifice area of the SJM valve, free of any struts, is separated into approximate thirds, with complete washing of each leaflet during the cardiac cycle. A slow cardiac rate or rhythm disturbance may produce occasional slight leaflet asynchrony, which is detectable by high-speed cinefilm or echocardiography(20,21). Since tissue valves are contra-indicated in children and young persons, especially due to their propensity to undergo calcification (see Chapter 12), the SJM valve may have an important role to play in this group of patients(12,22-26).

Thrombotic occlusion of a SJM prosthesis in the mitral position has been reported from our institution(27) and in the tricuspid position from elsewhere(28). In the present study, 4 patients had thrombotic obstruction of St Jude Medical prostheses : one tricuspid and 3 mitral prostheses were thrombosed. One of the patients with a thrombosed SJM mitral prosthesis had suffered from severe myocardial failure. From Australia, Hunt et al.(29) reported that thromboembolic complications occurred less frequently in patients with St Jude valves than in reports of similar patients with other

prostheses, provided that anticoagulation was maintained. Jones(30) warned that only small amounts of thrombotic material accumulating at critical points may cause failure of this prosthesis. Baudet et al.(31) reported a patient,who was not on anticoagulant therapy and thrombosed a SJM mitral valve prosthesis. Moulton et al.(32) reported a case of fatal thrombosis of a SJM valve in the aortic position despite documented "therapeutic" levels of warfarin anticoagulation. They suggest that special attention should be paid to valve orientation at the time of surgery and possible septal impingement on the prosthetic leaflets. It is apparent that the SJM valve shares the propensity of other mechanical valves to initiate thrombosis.

Ziemer et al.(33) reported an intrinsic manufacturing fault in a SJM valve. Minimal disproportion between the leaflets and the valve ring caused intermittent inhibition of leaflet motion and the patient required re-operation. Guttierez et al.(34) reported a patient with a peri-prosthetic leak, which mimicked entrapment of a leaflet in a SJM mitral valve prosthesis. Other reported complications include partial detachment of a SJM aortic valve(35) and escape of a leaflet from a SJM mitral prosthesis due to a fracture in the pivot area(36). Kafka et al.(38) attributed the malfunction of their patient's SJM mitral prosthesis to lack of adequate anticoagulation plus impingement by a piece of papillary muscle on the prosthesis. Joyce et al.(39) successfully dissolved thrombus on a thrombosed SJM tricuspid valve in a 16-month-old child and restored normal valve function.

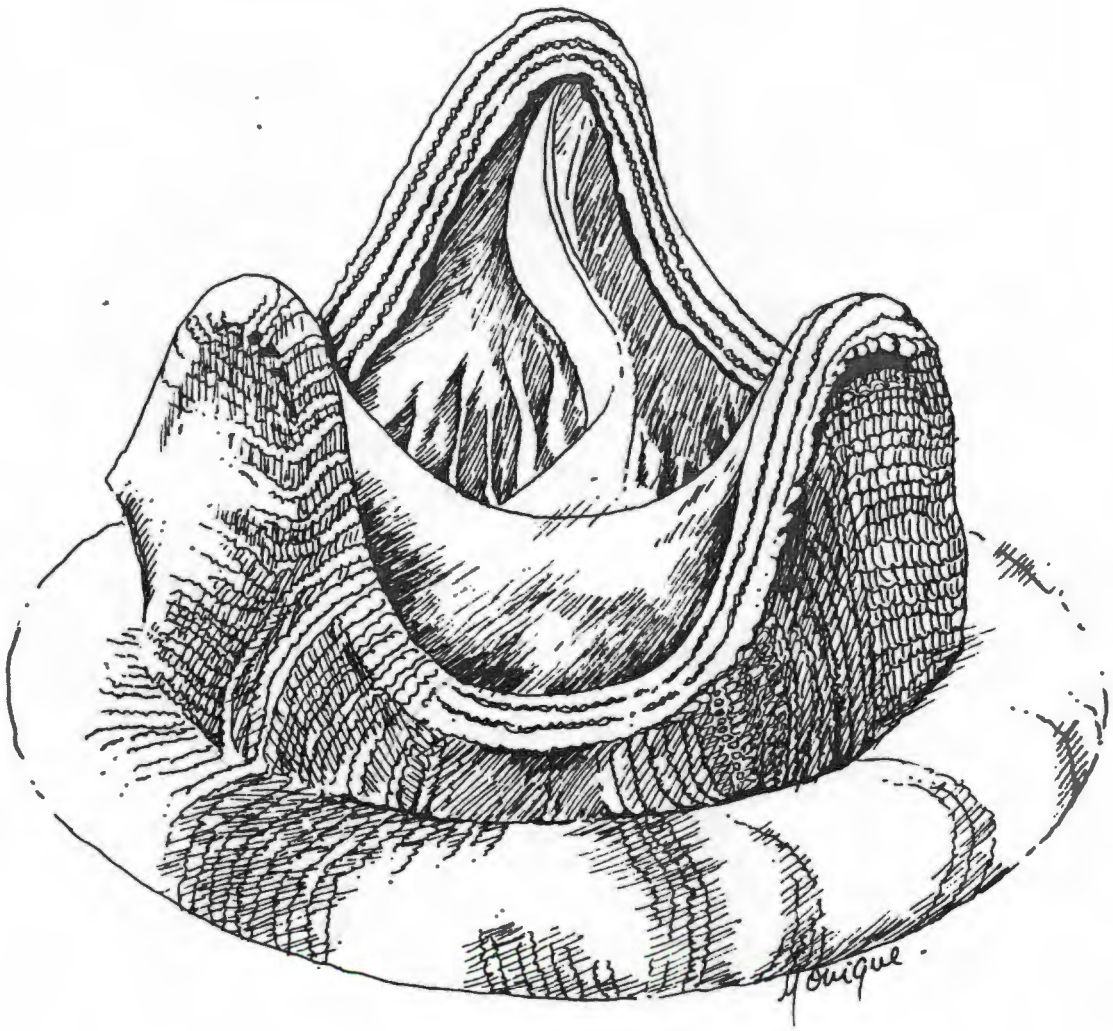
Horstkotte et al.(40) found that thromboembolic complications were significantly more frequent after Bjork-Shiley mitral, aortic and double valve replacements than after St Jude valve implantations. Wada and Kasagi(41) reported 3.7 thromboembolic episodes per 100 patient-years in their experience with 132 implanted SJM prostheses. Three of the 5 thromboembolic episodes were considered to be due to poor anticoagulation control and the cause was unknown in 2

instances. Duncan et al.(42) implanted 261 SJM valves in 253 patients over a 25 month period. There were 4 non-fatal thromboembolic episodes during the follow-up period, resulting in a risk of thromboembolism for aortic and mitral valves of 2.1% and 2.1% per patient-year respectively.

The Proceedings of the Third International Symposium on the St Jude Heart Valve held in November 1982 in Scottsdale, Arizona have recently been published(43). In this Symposium DeBakey et al.(44) stated that the principal disadvantages of the SJM valve are firstly, the poor design of the valve holder, and secondly the need for long-term anticoagulation. Nicoloff et al.(45) noted a low incidence of bacterial endocarditis and thromboemboli and an absence of mechanical failure. D'Alessandro et al.(46) established that the SJM valve is durable for at least 4 years. Sauvage(47) found that there are no significant differences regarding hospital mortality for the old-style Bjork-Shiley, the St Jude, or the Hancock valves. However, valve-related deaths within 2 years are higher in the patients with Hancock valves compared to those with Bjork-Shiley or SJM valves. Jones et al.(48) reported that the complication rate with the St Jude valve is as low or lower than that for any other mechanical prosthetic cardiac valve available in the world today.

For further discussion regarding the pathology of heart valve replacement with the St Jude Medical prosthetic cardiac valve please see Chapter 18.

TISSUE VALVES



CHAPTER 9.

PATHOLOGY OF THE UNIVERSITY OF CAPE TOWN FORMALDEHYDE-TREATED PORCINE XENOGRAFT XENOGRAFT BIOPROSTHESIS

CHAPTER 9.

PATHOLOGY OF THE UNIVERSITY OF CAPE TOWN FORMALDEHYDE-TREATED PORCINE XENOGRAFT BIOPROSTHESIS

The mitral valve was replaced by a formaldehyde preserved, stent-mounted porcine aortic valve in 33 patients at Groote Schuur Hospital. No accurate data are available regarding the period of implantation of these xenografts, but the majority had been implanted for less than 18 months. Usually, there was a gradual onset of dysfunction of the prosthesis, which allowed for timeous replacement of the failed xenografts by another valve substitute(1). Eleven of the failed xenograft prosthetic valves were submitted for pathological examination. Since there were only two autopsies on such patients with malfunctioning xenograft valves, the standard approach used in the present study of the major complications relating to prosthetic valve replacement could not be applied. The nature of the dysfunction of the xenograft valves which necessitated their removal will be described below.

The eleven patients ranged in age from 18 to 59 years. The valves had been in situ for a mean period of 9.9 months (S.D.= 8.6) and the range was from 2 to 32 months. Table 9.1 summarizes the main clinical and pathological details of the 11 patients. The most important macroscopical finding was that all of the cusps of the implanted xenograft prostheses showed varying degrees of stretching and deformation with resultant valvular incompetence. No cusp had perforated and no thrombi were seen with the naked eye. A prosthesis which had been implanted for 32 months showed a torn commissure (Fig. 9.1). However, microscopically 8 of the 11 valves had a thin layer of platelet-fibrin thrombus on the arterialis (concave) surface of the cusps. Histologically, all of the grafted valves showed an absence of the original cells of the cusp. Several cusps had a few isolated mononuclear cells scattered

on their surface, often entrapped within the fibrinous deposit.

A variable reduction in amount of the cuspidal collagen was noted in each of the 11 valves. The collagen acquired an amorphous, hyaline or fibrinoid appearance and stained less intensely with the van Gieson stain. The fibrosa was often no longer distinguishable as a

Figure 9.1 : UCT formaldehyde-preserved porcine aortic valve xenograft prosthesis shows shortened, downward prolapsing cusps plus one torn commissure.

TABLE 9.1 : CLINICOPATHOLOGICAL DETAILS OF 11 PATIENTS WHOSE FAILED XENOGRAFTS WERE EXAMINED.

PATIENTS			PIG AORTIC VALVE GRAFTS				
					MICROSCOPIC APPEARANCE		
No.	AGE	SEX	DURATION (MTHS)	MACROSCOPIC APPEARANCE	CELLS	COLLAGEN REDUCTION	THROMBUS
1	20	F	2	*	SURFACE	++	NIL
2	56	F	3	*	+++PLASMA CELLS	+	NIL
3	23	F	4	*	SURFACE	++	+
4	59	F	4	*	NIL	+	+
5	49	M	4	*	NIL	++	+
6	25	M	9	*	SURFACE	+TWO CUSPS ++ONE CUSP	+
7	43	F	12	*	SURFACE	++	+
8	42	M	12	*	NIL	++	+
9	18	F	13	*	SURFACE	+	+
10	40	F	14	*	SURFACE	+	NIL
11	58	M	32	*T	+PLASMA CELLS	+	+

+=SCANTY, ++=MODERATE, +++=NUMEROUS,*=ALL CUSPS SHOWED VARYING DEGREES OF STRETCHING WITH RESULTANT VALVULAR INCOMPETENCE,T=TORN COMMISSURE

distinct layer within the cusp. An immune-mediated cellular response to the graft was noted in two valves only (cases 2 and 11). The pathology of valves which failed early (four months or less after insertion) was the same as those failing later (after nine months).

Striking differences were noted when the failed xenograft valves were compared macroscopically and microscopically with the control pig valves. The cusps of the control valves meet together in a triradiate fashion with a fairly wide area of apposition and have clearly discernible valve pockets. The contact areas of the cusps lie in a vertical plane at a level superior to that of the sewing ring. The failed xenograft valves had stretched cusps, which hanged down below the level of the sewing ring and rendered the valve incompetent. In a few of the xenografts one cusp (often the one with muscle in its base) showed a greater degree of prolapse than did the other two. The pig aortic valve has an essentially similar histology to that of the human aortic valve (2). The anatomy of the pig aortic valve differs from that of the normal human aortic valve in that one-third of the porcine aortic ring is formed by cartilage and the base of the right coronary cusp is muscular(3). The °backbone' of the normal pig aortic valve cusp consists of a layer of compacted collagen fibres called the fibrosa. The remainder of the cusp is composed of loosely arranged collagen and elastic fibres. Moderate numbers of fibroblasts are present.

The host cellular response in 9 of the 11 cases was that of a mild mononuclear cellular infiltration at the base of the cusp where it had been in proximity to the host tissue. There was no sign of an host immune response to the acellular, denatured collagen of the cusp in these 9 valves. In the remaining two xenografts the cellular response was more florid and there were indications of a possible host immune response as evidenced by the presence of plasma cells and other pyroninophilic cells of lymphoid type. These cells were most numerous at the base of the cusp and appeared to be migrating

out along the cusp surface in diminishing numbers towards its free margin. The cellular infiltrate was associated with erosion of the cuspidal substance in areas. Apart from this response by what appear to be immunologically competent cells, the cusps of these two patients did not appear to show any signicant differences from the other nine cases which failed to evoke a similar response.

There was no sign of infection of any of the grafted valves. In contrast to the collagen, the elastic tissue of the heterograft valve cusps had a relatively normal appearance. No abnormality of acid mucopolysaccharide production was noted. None of the valves showed any evidence of calcification.

Electron microscopy of the control pig valves revealed that the collagen fibres were poorly preserved, but their structural integrity appeared to be intact and a regular periodicity was still discernible in most of the fibres (Figure 9.2). The collagen fibres of the xenograft valve of patient 10 had an ultrastructural appearance similar to that of the controls. However, electron microscopy of the collagen present in the valve of patient 2 (one of the two valves eliciting an immune response) revealed that the poorly preserved collagen fibres in many areas seemed to °fade out' and merge with amorphous, finely granular material lying between still intact collagen fibres (Figure 9.3). Periodicity was discernible in very few of the fibres. It is likely that the amorphous, finely granular material is derived from the destruction of collagen fibres. Electron microscopy of areas of total loss of collagen revealed finely granular material in the region normally occupied by well-orientated bundles of collagen fibres.

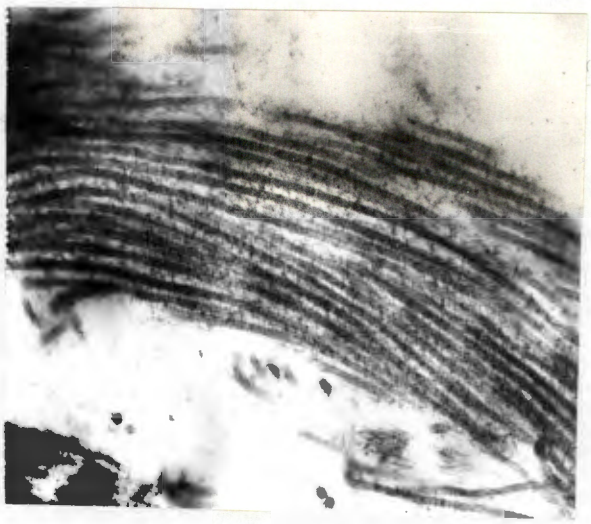


Figure 9.2 : Regular periodicity is discernible within some of the collagen fibres of an unused formaldehyde-preserved UCT xenograft valve. (Electron photomicrograph, X 127000).

Figure 9.3 : Poorly preserved collagen fibres of the xenograft which had been implanted in patient 2 for 2 months. Periodicity is lacking and the fibres appear to be disintegrating into amorphous, finely granular material. (Electron photomicrograph, X 190000).

COMMENT

Stretching of the valve cusps was the cause of the incompetence in all 11 failed aortic valve xenografts, with a torn commissure contributing to the regurgitation in one patient. Tearing of the substance of the cusps was not noted. The changes observed in the collagen seem to be the most significant. The denatured collagen of the xenograft has a low antigenicity and limited durability. Progressive weakening of a valve subjected to an abnormal degree of stress is the likely cause of the observed changes. A similar problem of stretching of aortic valve homograft cusps was encountered by Davies et al.(4). In the discussion of a paper by Carpentier et al.(5), Kay states that "all transplant valves in patients six months or more who come to autopsy ...demonstrated varying degrees of stretching of the leaflets, attenuation of the tissues, fragmentation and laceration regardless of the method of preservation or whether it was a homograft or heterograft. One of the factors responsible for failure may well be the inability of the aortic valve to withstand the greater ventricular closing pressures over a prolonged period without becoming stretched." Our experience in these 11 patients(6) is similar to that of Wright et al.(7) and Stimmel et al.(8) who reported that implanted formalin-preserved porcine xenograft valves showed valvular insufficiency in 35% of cases within one year of operation because of tissue disruption.

While there are many instances, both physiological and pathological, in which collagen is rapidly destroyed(9-11), it appears unnecessary to postulate active collagenolysis of the cuspidal collagen of the failed xenografts. The inert and denatured collagen in the transplanted pig valve does not have an infinite durability. No living cells are present within the valve substance, thus no new collagen can be produced. The destruction of the valvular collagen, which is not prevented by the formaldehyde treatment, is a function of time, augmented perhaps by the increased mechanical stress that the

valve is subjected to in the mitral position. Treatment of the pig aortic valve in formaldehyde renders the cusps more rigid than they are in the fresh state. Gunning and Meade(12) feel that once the valve cusps are thickened or changed by preservation then turbulence ensues. If turbulent flow is present, the natural deterioration that occurs in preserved valve cusps may well be accelerated.

The use of formalin (4% formol-saline) is an easy means of attaining bacteriological sterility as well as attenuation of antigenicity of the valvular collagen. None of the University of Cape Town formaldehyde-treated porcine valves were complicated by infective endocarditis. This contrasts with 7 instances of infection among 30 orthotopically transplanted human homograft aortic valves sterilized with betapropiolactone reported by Reichenbach et al.(13) and infection of some of the early aortic homografts treated with steroids by Davies et al.(4). Thrombus was detectable only microscopically on the cusps of our patients' xenografts. The latter finding contrasts with the experimental work in dogs of Gunning and Meade(12), who noted that pig valves preserved in formaldehyde showed a tendency for thrombus formation in the sinuses of Valsalva.

Ionescu et al.(14) postulated that calcification would be less prone to occur due to the low pH inside the formaldehyde-treated transplant. The present results would appear to confirm this, as the absence of calcification was a constant finding in each of the 11 xenografts examined. This contrasts with the relative frequency with which calcification has been observed in aortic homograft valves transplanted in the fresh state(4,15). Mohri et al.(16) found foci of apparently reversible mineralization in fibrin deposits on homograft aortic cusps in the dog ; the valves had been transplanted fresh and still contained viable donor cells. It is doubtful that the pH within the formalin-treated xenograft

aortic valve cusps would remain low for many months, since the valve is in intimate contact with the circulating blood. Our 11 xenografts had been in situ for a mean period of only 9.9 months ; this short period may also be a factor in the lack of calcification of these valves.

Another possible explanation for the absence of calcification may be that formaldehyde acts as a tanning substance by combining readily with the epsilon-amino group of the lysine residues in collagen with the formation of a methylol compound(17). These groups, which are important in tissue mineralization such as calcification, may thus be blocked by the action of the formaldehyde. As we shall see later (Chapter 12), cuspidal calcification is a serious complication limiting the use of glutaraldehyde-treated porcine aortic valve xenografts in young persons. Manufacturers of glutaraldehyde-preserved porcine bioprostheses are currently trying to devise means of lowering the calcification-promoting effects of the glutaraldehyde fixation procedure. The latter has proved superior to formaldehyde treatment with regard to bioprosthetic durability.

The absence of any significant immune response in 9 of the 11 transplanted valves agrees with the suggestion of others(18) that the reason for this lies in the nature of the cuspidal tissue, which is low in cell membrane elements, contains denatured protein and is a non-living graft. Collagen possesses a low antigenicity even if untreated. This premise has been borne out by cardiac transplantation in which the donor myocardium readily evokes a rejection response on the part of the host, whilst the donor heart valves seldom stimulate rejection. Hirsch(19) suggested that autograft, homograft and xenograft valves should all behave similarly in failing to evoke a destructive immunological or inflammatory response in the host. My findings in 9 of the 11 valves confirm this with regard to porcine xenograft valves. The reason for the plasma cell response in two of the valves is

unexplained.

The microscopical and ultrastructural findings suggest that the cuspidal stretching results from a depletion of collagen fibres which disintegrate into amorphous, granular debris. Similar appearing material was described in extracellular collagen resorption in carrageenin granulomas(9) and in a report on connective tissue abnormalities in spontaneous rupture of chordae tendineae(20). Apart from the lack of durability, the formaldehyde-treated porcine xenograft aortic valve has several advantages over mechanical prosthetic heart valves, especially with regard to thromboembolism, even if no anticoagulation is given. It was hoped that a living autologous fascia lata valve would retain the advantages of the pig valve, while possessing a greater inherent durability by virtue of its living fibroblasts. However, in practice the fascia lata valve became depleted of fibroblasts and the collagen degenerated(21,22). Insufficiency of the implanted valve together with thromboembolic complications were frequent.

CHAPTER 10.

PATHOLOGY OF CARDIAC VALVE REPLACEMENT WITH THE HANCOCK PORCINE XENOGRAFT BIOPROSTHESIS

CHAPTER 10.

PATHOLOGY OF VALVE REPLACEMENT WITH THE HANCOCK PORCINE XENOGRAFT BIOPROSTHESIS

The yearly survival rates for patients who had Hancock cardiac valvular prostheses implanted at Groote Schuur Hospital are indicated in Table 10.1. The post-implantation embolism events are given in Table 10.2.

MITRAL VALVE REPLACEMENT

Only eight patients with Hancock mitral valve bioprostheses were autopsied. Their mean age was 38.9 years (S.D.= 19.4 years) with a range of 16-63 years. There were 5 coloureds, 2 blacks and 1 white patient. Four patients were males and 4 were females. The mean post-operative survival period was 95.4 days (S.D.= 171.1 days) with a range of 0-318 days. The mean heart weight was 583 grams (S.D.= 152 grams) with a range of 371-826 grams. In 7 of the 8 patients the pre-operative valvular disease had a rheumatic aetiology ; one patient had mitral incompetence due to rupture of an infarcted papillary muscle. The principal causes of death in these patients are indicated in Table 10.3.

One death was attributable to an error in pre-operative diagnosis : the patient was found to have severe, unrelieved aortic stenosis at autopsy 2 weeks after mitral valve replacement. Another patient died because of an error in operative technique, whereby excision of a calcified mitral valve had led to loss of atrio-ventricular continuity when portion of the mitral valve ring was also excised. Death was due to cardiac tamponade, which followed massive bleeding through the resultant defect. Initially the haemorrhage was retained by the epicardium and the patient died 3 hours after the operation(1). The role which loss of atrio-ventricular

continuity may play in the development of submitral aneurysms is discussed in Chapter 17. A death occurred due to a problem inherent in the Hancock bioprosthesis ; severe mitral stenosis resulted from cuspidal calcification in the xenograft.

TABLE 10.1 : YEARLY SURVIVAL AFTER IMPLANTATION OF HANCOCK PROSTHESES (1976 - 1982)

YRS. AFTER OP.	LIVE PTS.	EVENTS	DEATHS	SURVIVE INCOMPLETE INTERVAL	REMOVED FOR NEW OP.	INTERVAL SURVIVAL PROPOR.	CUMUL. SURVIVAL RATE
0-1/12	306	0	21	0	3	0.931	0.931
1/12-1	255	0	12	72	2	0.945	0.880
1-2	169	0	4	50	3	0.972	0.855
2-3	112	0	4	26	1	0.959	0.820
3-4	81	0	2	22	2	0.971	0.796
4-5	55	0	3	19	3	0.932	0.742
5-6	30	0	1	6	1	0.962	0.714
6-7	22	0	1	5	4	0.943	0.673

TABLE 10.2 : EMBOLISM EVENTS AFTER IMPLANTATION OF HANCOCK PROSTHESES (1976 - 1982)

YRS. AFTER OP.	EVENT-FREE PTS.	EVENTS IN INTERVAL	EVENT-FREE DEATHS	SURVIVE INCOMPLETE INTERVAL	REMOVED FOR NEW OP.	INTERVAL SURVIVAL PROPOR.	CUMUL. EVENT-FREE RATE
0-1/12	294	2	20	0	3	0.993	0.993
1/12-1	242	3	12	69	2	0.985	0.978
1-2	156	5	4	45	3	0.962	0.941
2-3	99	6	3	25	1	0.929	0.874
3-4	64	4	0	20	0	0.926	0.809
4-5	40	2	0	15	1	0.937	0.758
5-6	22	1	0	4	0	0.950	0.720
6-7	17	0	0	4	4	1.000	0.720

TABLE 10.3 : PRINCIPAL CAUSES OF DEATH (1 PER PATIENT) IN 8 PATIENTS WITH HANCOCK MITRAL VALVE PROSTHESES.

NO CAUSE FOUND	3
CALCIFIED HANCOCK XENOGRAFT	1
POOR PRE-OPERATIVE CONDITION	1
UNOPERATED SEVERE AORTIC STENOSIS	1
MYOCARDIAL NECROSIS	1
SURGICAL DISRUPTION OF VALVE RING	1

TABLE 10.4 : NON-FATAL COMPLICATIONS/ASSOCIATED DISEASES IN 8 PATIENTS WITH HANCOCK MITRAL VALVE PROSTHESES.

SMALL HAEMOPERICARDIUM		1
SUBAORTIC STENOSIS DUE TO PROSTHESIS		1
TORN LEFT ATRIAL APPENDAGE		1
MASSIVE LEFT ATRIAL THROMBUS		1
SUTURE IN CORONARY ARTERY		1
XENOGRAFT CUSPIDAL PROLAPSE		1
ORGAN INFARCTS:		
	Kidney	2
	Spleen	2
	Brain	2
	Lung	1
	Heart (subendocardial)	1

No recognizable direct post-operative complications were encountered. Two deaths were due to complications which were unrelated to the cardiac operation : one suffered a myocardial infarction due to atherosclerosis, and the other was in a very poor general condition before being operated upon as an

emergency. No morphological cause of death was found in the remaining 3 patients (arrythmia cannot be excluded). Non-fatal complications are listed in Table 10.4. Only one of the 8 Hancock prosthetic valves had thrombus on it. The thrombus was situated on the atrial side of the sewing ring and between one stent of the prosthesis and the left ventricular wall.

AORTIC VALVE REPLACEMENT

A solitary patient was encountered at autopsy with a Hancock valve prosthesis in the aortic position. The patient, a 68-year-old white male with medionecrosis of the aorta, developed aortic incompetence due to dilatation of the aortic ring. The aortic valve was replaced by a No. 27 Hancock prosthesis. The post-operative course was uneventful. Seven and a half months after the surgery he was re-admitted with severe chest pain and died of a ruptured dissecting aneurysm of the aorta. The Hancock prosthesis showed no abnormality. The heart weighed 670 grams and showed sub-endocardial fibrosis plus focal myocytolysis.

DOUBLE VALVE REPLACEMENT

Three patients had Hancock prostheses inserted in both the aortic and the mitral position for rheumatic valvular disease. The first patient was a 22-year-old black male with aortic incompetence, mitral incompetence (mild mitral stenosis) and functional tricuspid incompetence. The patient did not survive the operation during which surgically produced complete heart block followed insertion of the mitral prosthesis. At autopsy the heart weighed 665 grams and the Hancock valves showed no significant abnormality. No principal cause of death was identified. Numerous proliferative phase Aschoff bodies were seen histologically. No organ infarcts were noted.

The second patient, a 37-year-old male with aortic

incompetence and mixed mitral valve disease, survived 13 days after mitral and aortic valve replacement. His heart weighed 824 grams and the Hancock aortic valve appeared normal. The mitral prosthesis was covered with abundant infected (Staphylococcus aureus) vegetations, which narrowed the effective orifice of the prosthesis by as much as 60%. Dehiscence had occurred at one side of the prosthesis, where sewing ring sutures had torn free from the infected host tissue. No organ infarcts were present.

The third patient, a 21-year-old male, with mixed aortic and mixed mitral valve disease, suffered severe acute myocardial ischaemic damage during cardiopulmonary bypass with coronary perfusion and survived only 3 hours post-operatively. Autopsy revealed extensive coagulative necrosis and coagulative myocytolysis (contraction band necrosis/myofibrillar degeneration) of his ventricular myocardium. No significant coronary arterial disease was present. His heart weighed 965 grams and the Hancock prostheses appeared normal. No organs showed infarcts.

The principal causes of death in the 12 patients with Hancock valve prostheses described above fell into the following categories : due to error in pre-operative diagnosis,1 ; due to error in operative technique,2 ; due to problems related to the prosthetic valve,2 ; due to post-operative complications,nil ; unrelated to the cardiac operation,3 ; and cause unknown,4. Prosthesis-related complications were the cause of only 17% of the 12 deaths, but the mean post-operative duration of the patients with implanted prostheses was only 83.5 days (S.D.= 149.2).

COMMENT

Many of the complications and comments which will be made in this section will be equally applicable to other tissue valves, especially the Carpentier-Edwards porcine aortic valve bioprosthesis (see Chapter 11). Cohn et al.(2)

compared the Hancock porcine valve prosthesis with a prosthetic Harken discoid valve for isolated mitral valve replacement. They concluded that there is a significant reduction in morbidity and mortality, primarily from reduced thromboembolism, if a porcine valve is used for mitral replacement. They recommend that anticoagulants should be used in patients with atrial fibrillation and enlarged left atria regardless of the type of valve used. In an editorial comment on a later report by from the same group(3), Kirklin(4) wondered whether elderly patients with bioprostheses should not also receive anticoagulants. Stahmann et al.(5) reported a patient with transient cerebral ischaemic attacks due to release of thrombi formed on the worn cloth covering of the supporting valve stent.

Unexplained primary thrombosis of a Hancock prosthesis has occasionally been encountered(6,7). Pipkin et al.(8) reported that only one of 6 late deaths of patients with Hancock prostheses was due to a valve-related problem. Their actuarial analysis predicted 84% survival at 3 years. Following on the favourable preliminary experience regarding the clinical course, thrombogenicity and durability of the glutaraldehyde-preserved porcine aortic valve(9-16), Lurie et al.(17) performed post-operative cardiac catheterization on 26 patients who had Hancock prostheses implanted for a mean period of 19 weeks. They concluded that these prostheses give generally satisfactory post-operative haemodynamic valvular function.

Cevese et al.(18) reported on 564 patients who had received Hancock cardiac valves for observation periods extending up to a maximum of 6.5 years. They concluded that the valve was durable for at least that period. Cohn et al.(19) and Casarotto et al.(20) came to similar conclusions after follow-up periods in excess of 5 years in large groups of patients. Gallo et al.(21) followed up 632 patients with Hancock valves, which had been implanted for periods of between 1 and 6 years and were encouraged by its durability

over that medium period. The same group again expressed optimism in a similar report 2 years later(22). Bolooki et al. (23), in evaluating failures of Hancock xenograft valves, presented data to show that valve position was an important determinant as to whether structural failure occurred or not. Structural failure was not observed after aortic valve replacement, whereas 8 mitral valve prostheses were removed for structural failure (calcification, leaflet perforation, or torn cusp) at a mean follow-up period of 42 months. Hannah and Reis(10) reported on 234 porcine xenograft valves implanted for up to 5 years. Twelve patients, all with mitral prostheses, had systemic arterial thromboembolism.

In an attempt to ameliorate the problem of residual systolic gradients and small effective orifice areas in the aortic position, Hancock Laboratories introduced a modified bioprosthesis, constructed by the removal of the muscular right coronary leaflet and replacing it with the non-coronary cusp from a second porcine aortic valve. Zusman et al.(24) found that the Hancock modified orifice valve has good hydraulic performance and a low embolic rate without the need for anticoagulation and it is acceptable for the elderly patient with a small aortic root.

Several reports document structural changes in Hancock valve prostheses(23,25-36). Spray and Roberts(25) observed the following histological changes in 44 bioprostheses : (i) fibrin deposits on the inflow and outflow surfaces of the cusps ; (ii) inflammatory cellular infiltrates ; (iii) histiocyte deposition ; (iv) giant cell formation and (v) focal disruption of the fibrocollagenous structure of the cusps. Their observations indicate that porcine bioprostheses are not biologically inert in the human circulation. Valve failure was rare up to the period of 72 months studied. Dysfunction of Hancock prosthetic valves due to degeneration, disruption and/or thrombosis has been documented by Hetzer et

al.(26), Brown et al.(27) and Thiene et al.(30). Bortolotti et al.(29) reported 2 cases of late Hancock prosthetic stenosis due to fibrous tissue overgrowth on the atrial aspect of the cusps. Schoen et al.(31) described a patient with the carcinoid syndrome who had his mitral and tricuspid valves replaced by Hancock valve prostheses. He died 8 months later of tumour-related complications and it was observed that carcinoid plaques had extended onto both prostheses from the atria.

Infective endocarditis of Hancock prostheses was described by Magilligan et al.(34) and Bortolotti et al.(35). Magilligan et al. reported 11 patients with infective endocarditis of their Hancock valves. There were 3 valve-related deaths : 2 from valve incompetence and 1 from mitral and aortic xenograft stenosis. These authors concluded that the Hancock porcine xenograft is (i) as resistant to infection as are rigid prostheses in active infective endocarditis ; (ii) resistant to early post-operative bacteraemias ; and (iii) easier to sterilize than rigid prostheses and more durable than other tissue valves (e.g., fascia lata, homograft or pericardial valves) in the face of prosthetic valve endocarditis. Bortolotti et al. studied 10 infected Hancock valves removed from 9 patients. The devices had been in place from 2 - 87 months (mean= 37.5) and the causative organisms included gram negative bacteria in 3 patients (Klebsiella, Enterobacter and Serratia), gram positive organisms in 2 patients (Staphylococcuc aureus and Streptococcus viridans) and fungi in 4 (Candida in 3 and an Aspergillus species in one). Prosthetic incompetence was the commonest type of dysfunction resulting from the infection. The mortality of prosthetic valve endocarditis is very high(37-39) and a high incidence of infection-related deaths has been reported when endocarditis involves porcine xenografts(35,40,41). This poor outcome might be due to a high incidence of associated septic complications. Only one out of my 12 autopsied patients with Hancock prostheses had infective

endocarditis and this led to partial dehiscence of the mitral prosthesis.

Left ventricular rupture, which may complicate mitral valve replacement, may result from excessive mitral valve excision, as was demonstrated by one of my patients. A second type of rupture that may occur with mitral valve replacement is illustrated by the 2 patients reported by Bortolotti et al.(42) who developed a deep erosion of the left ventricular free wall, which evolved into a cardiac rupture in one of them. The laceration is ascribed to friction between a prosthetic strut and the endomyocardium. A disproportion between °°high-profile" device and the left ventricular chamber is the likely cause of this complication.

Salomon et al.(28) reported an unusual complication of the Hancock valve, namely strut compression by a too small aortic root resulting in the struts being angled centrally into the aortic lumen. Impedance of central flow had led to subsequent valve thrombosis. In a similar case reported by Magilligan et al.(43) the inward bending of the stents was associated with severe haemolysis. I have encountered one surgically excised Hancock aortic valve prosthesis which showed similar strut deformation. The prosthesis was free of thrombus, having been removed due to a cuspidal tear four years after implantation and the patient had no overt haemolysis. Borkon et al.(32) noted similar inward stent-post bending of a mitral Hancock porcine bioprosthesis 9 years post-operatively, which they attributed to "polymer creep." The latter is an aging characteristic of polypropylene(44). Spray and Roberts(25) observed stent-post deformity associated with bioprosthetic failure due to leaflet degeneration, but they did not discuss its significance.

Arbustini et al.(33) described a case in which lipid infiltration of the cusps of a Hancock mitral valve prosthesis 8 years after implantation was so diffuse and severe that it, by itself, led to commissural detachment and significant valve incompetence. Histology revealed cholesterol clefts in the

spongiosa and fibrosa, interspersed with amorphous material. Scanning electron microscopy showed erythrocytes, platelets and macrophages on the cuspidal surface which was partially devoid of endothelial cells. Transmission electron microscopy revealed large lipid droplets between bundles of collagen fibres.

Pre- and post-implantation ultrastructural changes in Hancock porcine valvular xenografts were described by Ferrans et al.(36). Unimplanted, commercially available valves showed loss of endothelium and acid mucopolysaccharides. Short-term post-implantation changes included insudation of plasma proteins, penetration of erythrocytes into surface crevices, formation of a thin surface fibrin layer and deposition of macrophages, giant cells and a few platelets. Longer-term changes consisted of progressive disruption of collagen, erosion of the valvular surfaces, platelet aggregate deposition and accumulation of lipid. They concluded that progressive breakdown of collagen is a critical factor in the long-term durability of glutaraldehyde-treated porcine valvular xenografts.

CHAPTER 11.

PATHOLOGY OF CARDIAC VALVE REPLACEMENT WITH THE CARPENTIER-EDWARDS PORCINE XENOGRAFT BIOPROSTHESIS

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PATHOLOGY OF CARDIAC VALVE REPLACEMENT WITH THE CARPENTIER-EDWARDS PORCINE XENOGRAFT BIOPROSTHESIS.

The yearly survival rates and embolism events in Groote Schuur Hospital patients with Carpentier-Edwards bioprostheses are listed in Tables 11.1 and 11.2 respectively.

AORTIC VALVE REPLACEMENT

Fifteen patients with isolated replacement of the aortic valve with a Carpentier-Edwards bioprosthesis were autopsied. Eleven patients died 30 days or less after operation (group 1) and only 4 died later (group 2) :

GROUP 1

These 11 patients had a mean age of 57.8 years (S.D.= 11.9) and their ages ranged from 39-82 years. There were 6 whites, 3 coloureds and 2 blacks. The pre-operative aortic valve lesions were as follows : aortic nodular sclerosis (senile calcific tricuspid aortic stenosis) 5 cases, aortic ring dilatation due to aortic aneurysm 4 cases, and 1 patient with Fallot's tetralogy had aortic valvular incompetence due to lack of cuspidal support associated with a peri-membranous ventricular septal defect. No information was available regarding the aetiology of the valvular disease in one patient. Post-operative survival ranged from 0.8 to 15 days, with a mean of 4.3 days (S.D.= 5.5). The mean heart weight was 644 grams (S.D.= 165) with a range of 463-940 grams. None of the 11 Carpentier-Edwards prostheses showed naked eye thrombus on the cusps or sewing ring. This group of patients exhibited the following organ infarcts : heart 3, renal 1, pulmonary 1, and cerebral infarction 1.

TABLE 11.1 : YEARLY SURVIVAL AFTER IMPLANTATION OF CARPENTIER-EDWARDS PROSTHESES (1976 - 1982)

YRS. AFTER OP.	LIVE PTS.	EVENTS	DEATHS	SURVIVE INCOMPLETE INTERVAL	REMOVED FOR NEW OP.	INTERVAL SURVIVAL PROPOR.	CUMUL. SURVIVAL RATE
0-1/12	706	0	43	0	3	0.939	0.939
1/12-1	637	0	28	33	4	0.955	0.897
1-2	572	0	21	50	10	0.961	0.862
2-3	491	0	14	50	17	0.969	0.835
3-4	410	0	10	74	10	0.973	0.812
4-5	316	0	9	114	12	0.964	0.783
5-6	181	0	6	101	15	0.951	0.745
6-7	59	0	4	43	4	0.887	0.661

TABLE 11.2 : EMBOLISM EVENTS AFTER IMPLANTATION OF CARPENTIER-EDWARDS PROSTHESES (1976 - 1982)

YRS. AFTER OP.	EVENT-FREE PTS.	EVENTS IN INTERVAL	EVENT-FREE DEATHS	SURVIVE INCOMPLETE INTERVAL	REMOVED FOR NEW OP.	INTERVAL SURVIVAL PROPOR.	CUMUL. EVENT-FREE RATE
0-1/12	629	8	39	0	3	0.987	0.987
1/12-1	557	14	27	13	4	0.974	0.961
1-2	499	25	11	26	8	0.948	0.911
2-3	429	11	9	39	11	0.972	0.885
3-4	359	17	5	64	6	0.947	0.838
4-5	267	13	3	101	9	0.938	0.786
5-6	141	5	1	78	11	0.948	0.745
6-7	46	1	2	35	3	0.962	0.717

GROUP 2

These four patients had a mean age of 43.7 years (S.D.= 14.2) and the range was 31-59 years. There were 2 whites and 2 coloureds ; all four were males. The aortic valvular disease necessitating operation was as follows : unknown 1, rheumatic fever 2, and aortic nodular sclerosis 1. The mean post-operative survival period was 106.8 days (S.D.= 119.2) with a range of 35-285 days. The mean heart weight was 728 (S.D.= 303) grams and the range was 460-1057 grams. Only 2 infarcts were encountered (lung 1, spleen 1). The prostheses were all free of macroscopical thrombotic deposits.

Tables 11.3 and 11.4 list the principal causes of death and major non-fatal complications/associated conditions in the 14 patients with Carpentier-Edwards aortic prostheses. Associated valvular disease took the form of mitral stenosis (2 patients), mitral incompetence (1 patient) and mixed mitral valve disease plus tricuspid incompetence (1 patient).

TABLE 11.3 : PRINCIPAL CAUSES OF DEATH (1 PER PATIENT) IN 5 PATIENTS WITH CARPENTIER-EDWARDS AORTIC VALVE PROSTHESES.

UNKNOWN	3
PROSTHESIS BLOCKS CORONARY OSTIUM	1
OPERATIVELY INDUCED MYOCARDIAL DAMAGE	2
IATROGENIC CORONARY DISSECTION	1
RUPTURED AORTOTOMY WOUND	3
CEREBRAL HAEMORRHAGE	1
MEDIASTINAL ABSCESS	1
MYOCARDIAL FAILURE	1
MYOCARDIAL INFARCTION (ATHEROSCLEROSIS)	1
TRAUMATIC DEATH	1

TABLE 11.4 : NON-FATAL COMPLICATIONS/ASSOCIATED CONDITIONS IN 15 PATIENTS WITH CARPENTIER-EDWARDS AORTIC PROSTHESES.

PATIENTS WITH CORONARY BYPASS VEIN GRAFTS		4
AORTIC MEDIONECROSIS		2
ACUTE PANCREATITIS		1
SUBARACHNOID HAEMORRHAGE		1
RENAL TUBULAR NECROSIS		1
WOUND SEPSIS		2
ACUTE GASTRIC EROSIONS		1
MALIGNANT HYPERTENSION		1
ASSOCIATED VALVULAR DISEASE		4
HAEMORRHAGE IN BUNDLE OF HIS		1
ORGAN INFARCTS		
HEART	3	
LUNG	2	
KIDNEY	1	
SPLEEN	1	
BRAIN	1	

All of the valve cusps of the prostheses implanted in the group 1 patients showed histologically well preserved cuspidal collagen with ghost outlines of the pre-existing fibroblasts and scanty fibrin deposits on both aspects of the cusps. No host immune assault was noted, but an occasional host monocyte or lymphocyte was attached to the cuspidal surface in at least one section of every valve examined. The 4 prostheses implanted in the group 2 patients who survived longer also

showed a well preserved collagenous fibrosa, but the cuspidal collagen in the prosthesis of the longest survivor (who was murdered 285 days post-operatively) stained less intensely with the van Gieson stain. A few valve cusps contained scanty interstitial fibrin deposits, but there was no sign of calcification or of infection. All valves were devoid of endothelial cells and only an isolated host cell was attached here and there to the cuspidal surfaces. No intra-cuspidal haematomas were seen.

MITRAL VALVE REPLACEMENT

Sixteen patients came to autopsy with Carpentier-Edwards mitral valve prostheses. Twelve patients died 30 days or earlier post-operatively (group 1) and 4 survived longer (group 2).

GROUP 1

The 12 patients comprising this group had a mean age of 36.2 years (S.D.= 13.7) and an age range of 16-62 years. There were 5 males and 7 females ; 6 were coloureds, 3 white and 3 were black. The pre-operative natural mitral valve lesions were as follows : unknown 2, rheumatic fever 9 and mitral incompetence due to myocardial infarction 1. Their mean post-operative survival was 7.7 days (S.D.= 8.4) with a range of 0.42-30 days. The mean heart weight was 526 grams (S.D.= 79) and the range was 386-640 grams. Four of the 12 Carpentier-Edwards mitral prostheses had macroscopical surface thrombi (2 on the sewing ring and 2 on the concave aspects of the cusps). The thrombus was scanty in both amount and extent and did not cause significant obstruction to the prosthetic orifice.

The following infarcts were exhibited by the 12 patients : left ventricle 2, brain 7, lung 1, and kidney 2. Five

patients had associated disease of the aortic valve (incompetence in 2 and stenosis in 3) and 5 showed tricuspid valvular disease. The latter took the form of incompetence in 3 and stenosis in two. Histologically, all of the prosthetic cusps showed well preserved collagen in the fibrosa, with no living cells within the cusp. Scanty acid mucopolysaccharide was demonstrable in the spongiosa of the porcine cusps. Scanty surface fibrin deposits were detectable focally on nearly all of the valves examined. No calcification was detected and none of the valves had elicited a foreign body giant cell response. Electron microscopy of 3 randomly selected prostheses which had been implanted for periods of 1 day, 8 days and 30 days respectively revealed normal-looking collagen fibres.

GROUP 2

The four group 2 patients had a mean age of 33 years (S.D.= 32) with a range of 13-70 years. There were 2 blacks, 1 coloured and 1 white patient. All 4 had undergone aortic valve replacement for rheumatic valvular disease. The mean post-operative survival was 1725 days (S.D.= 430) with a range of from 1170-2220 days. Two of the 4 prostheses showed surface thrombotic deposits ; scanty fibrin-platelet deposits on the sewing ring in one patient and abundant similar thrombus filled the concavities of the three cusps in another. Only one infarct was noted in the 4 patients and this involved the brain. All four porcine valves had poorly preserved cuspidal collagen which stained weakly or not at all with the van Gieson stain. Focal fibrin deposits permeated the interstitium of the cusps and there appeared to be a total loss of acid mucopolysaccharide. No intra-cuspidal haematomas were seen. Electron microscopy performed upon a porcine valve which had been implanted for 1740 days revealed evidence of focal dissolution of collagen fibres into granular, amorphous, electron dense material.

Tables 11.5 and 11.6 list the principal causes of death and major non-fatal complications/associated conditions in the 16 patients with Carpentier-Edwards mitral prostheses.

TABLE 11.5 : PRINCIPAL CAUSES OF DEATH (1 PER PATIENT) IN 16 PATIENTS WITH CARPENTIER-EDWARDS MITRAL VALVE PROSTHESES

UNKNOWN	6
OPERATIVE AIR EMBOLISM	1
INFECTION	1
CALCIFIED XENOGRAFT	1
CEREBRAL THROMBOEMBOLISM	3
CEREBRAL HAEMORRHAGE	1
MEDIASTINITIS,SEPTICAEMIA	1
MYOCARDIAL FAILURE	1
SUICIDE	1

TABLE 11.6 : NON-FATAL COMPLICATIONS/ASSOCIATED CONDITIONS IN 16 PATIENTS WITH CARPENTIER-EDWARDS MITRAL PROSTHESES

DIGITALIS TOXICITY	1
CORONARY ARTERIAL THROMBOEMBOLUS	1
SUBAORTIC STENOSIS DUE TO PROSTHESIS	1
HAEMATOMA DISRUPTS THE BUNDLE OF HIS	1
ACUTE GASTRIC EROSIONS	1
SEPTUM PRIMUM ANEURYSM	1
ABDOMINAL ATHEROSCLEROTIC AORTIC ANEURYSM	1
VENOUS MALFORMATION OF RIGHT ATRIUM	1
CORONARY SAPHENOUS VEIN BYPASS GRAFT	1
BRONCHOPNEUMONIA	1
MARKED PASSIVE VENOUS PULMONARY HYPERTENSION	3
SIGNIFICANT CORONARY ARTERIAL DISEASE	2
ORGAN INFARCTS	
BRAIN	8
HEART	2
KIDNEY	2
LUNG	1

MORE THAN ONE CARPENTIER-EDWARDS VALVE PROSTHESIS IN THE SAME HEART.

Only seven patients with more than one Carpentier-Edwards prosthetic heart valve in the same heart were autopsied.

GROUP 1

Six of the patients fell into group 1 (death occurring one month or less post-operatively). They consisted of 4 males and 2 females (3 coloureds, 2 blacks and 1 white subject). Their mean age was 29 years (S.D.= 14.3) and the range was 14-51 years. The mean heart weight was 652 grams (S.D.= 165) with a range of 330-790 grams. The mean post-operative survival of the 6 patients was 2.2 days (S.D.= 2.4) and the range was 0.2-6.0 days. One patient had both the aortic and the mitral valves replaced ; three patients had their aortic, mitral and tricuspid valves replaced, and the remaining 2 patients had both their mitral and tricuspid valves replaced. The aetiology of the native heart valve disease necessitating operation was rheumatic fever in 5 instances and the sixth patient had myxomatous degeneration of the aortic and mitral valves. None of the 15 prostheses examined showed macroscopically detectable thrombi on the surface of the prosthesis.

Histological examination showed essentially similar features to those observed in the group 1 patients with Carpentier-Edwards aortic and mitral prostheses described above. The principal cause of death in the 6 group 1 patients with more than one Carpentier-Edwards bioprosthesis in the same heart was as follows : the cause of death was unknown in 5 patients, and one other patient died of a fungal infection superimposed upon bilateral pulmonary infarcts. The infected infarcts had developed prior to open heart surgery. There was no sign of infective endocarditis. No other organ infarcts were noted in these patients. Non-fatal

complications/associated conditions observed in the group 1 patients included the following : marked passive venous pulmonary hypertension in 2, pre-operative multiple lung abscesses in 1 patient, localised dissection of the aortic root below the aortotomy wound 1 patient, and one patient had focal deep oesophageal ulceration which may have resulted from a cautery electrode touching the lead of the intra-oesophageal temperature-monitoring device during surgery.

GROUP 2

Only one patient with more than one implanted Carpentier-Edwards prosthesis fell into the longer surviving group. The patient was a 14-year-old coloured female who died suddenly while at school 391 days after replacement of her aortic and mitral valves by Carpentier-Edwards prostheses for chronic rheumatic heart disease. At autopsy her heart weighed 380 grams and the most significant finding was that the mitral bioprosthesis had undergone extensive calcification resulting in severe mitral stenosis. Scanty fibrin-platelet thrombi were noted on the concave (non-contact) aspects of both bioprostheses, but there was no evidence of calcification of the aortic prosthesis, which had been implanted at the same time as the calcified mitral prosthesis.

PATHOLOGY OF SURGICALLY RESECTED CARPENTIER-EDWARDS VALVULAR PROSTHESES

A total of 10 Carpentier-Edwards prosthetic valves was submitted for pathological evaluation following surgical removal for prosthetic dysfunction. Eight valves had been implanted in the mitral position, and two in the aortic position. The patients' ages ranged from 13 to 56 years at the time of initial operation, with a mean of 36 years (S.D.= 16). Half of the patients were males. The prostheses had been implanted for periods ranging from 2-60 months (mean= 41

months).Five of the prosthetic valves were removed because of pure incompetence, one showed stenosis only, and 2 showed both stenosis and incompetence. Three of the 5 incompetent valves had tears near the commissures (type I lesion of Ishihara et al.(1)), and the other 2 had tears and/or holes in the cuspidal substance (types III and IV lesions of Ishihara et al.(1)). Three valves showed cuspidal calcification,(Fig. 11.1 and see Chapter 12 too). These three patients were aged 13, 14, and 16 at the time of their initial operation. Three valves showed scanty surface fibrin deposits and one aortic prosthesis (Fig. 11.2) was removed 3 years after implantation, because of massive thrombosis(2). The latter patient had received no anticoagulants post-operatively. One valve showed resolving infection of the cusps. In valves implanted for up to 36 months the collagen appeared histologically normal, but by 60 months there was a uniformly severe depletion of cuspidal collagen.

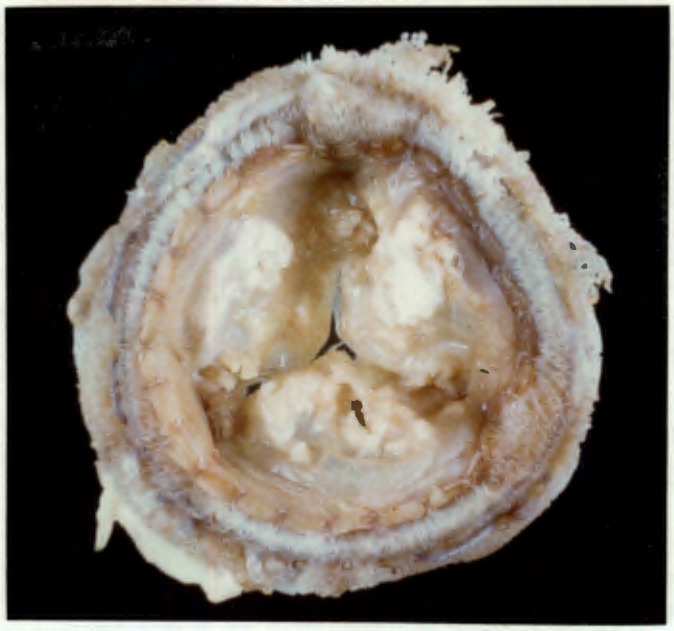

Figure 11.1 : Surgically excised calcified Carpentier-Edwards prosthesis 23 months after implantation. One cusp has two tears in its substance.

Figure 11.2 : Massive thrombotic deposits fill the cuspidal pockets of this Carpentier-Edwards aortic valve prosthesis. Contrary to the usual policy, the patient was given no anticoagulant in the initial post-operative period.

SUMMARY OF PRINCIPAL CAUSES OF DEATH IN ALL PATIENTS WITH CARPENTIER-EDWARDS PORCINE XENOGRAFT BIOPROSTHESES.

The principal causes of death in my 38 patients with Carpentier-Edwards porcine aortic valve xenograft prostheses fell into the following categories :
(i) error in pre-operative diagnosis,nil ; (ii) error in operative technique,5 ; (iii) prosthesis-related problems,9 ; (iv) general post-operative complications,6 ; (v) unrelated to cardiac operation,4 ; and (vi) unknown causes,14.

COMMENT

Between March 1975 and January 1978, an estimated 8,000 Carpentier-Edwards bioprostheses had been implanted world-wide(3) and the following complications had been reported to the manufacturers, Edwards Laboratories : endocarditis 5, high gradient 5, thromboembolism 5, thrombosis 5, prosthetic calcification by the 17th post-operative day 1, peri-prosthetic leak 1, leaflet perforation 6 (related to handling with surgical instruments), haemolysis 1, regurgitation 2 (due to stent distortion produced by sutures, which spanned distances greater than 5mm), miscellaneous 9 (e.g.,sewing ring disruptions and loosening of tissue-to-stent suture line). In November 1978, Edwards Laboratories reported that 0.625% glutaraldehyde was an effective sterilizing agent against the following organisms : Eschericia coli, Staphylococcus aureus, Streptococcus pyogenes, Candida albicans, Propionibacterium acnes, Bacillus subtilis, five species of Mycobacterium and Aspergillus species. It was concluded that 0.625% glutaraldehyde is effective against most organisms and only the mature spore of Chaetomium globosum was

resistant to such treatment(4). Formaldehyde in a 4% concentration was found to be an effective sterilizant against Chaetomium globosum in its mature spore form. Experiments with C14-labelled formaldehyde showed that formaldehyde was not incorporated into the protein structure of the glutaraldehyde-treated valve.

Haemodynamic studies(5) comparing Hancock and Carpentier-Edwards bioprostheses revealed that Carpentier-Edwards prostheses had significantly lower trans-valvular gradients than the Hancock valves(6) and the differences in the design of bioprosthetic valves and that of natural valves are probably major factors in increasing the stress in the bioprostheses(7). Echocardiography(8,9) has been useful in evaluating porcine aortic bioprostheses and detecting degeneration of such valves(10,11), vegetations(12,13), dehiscence(14,15) and flail porcine valve leaflets(16).

Clinical experience with the Carpentier-Edwards xenograft valve prosthesis indicated that it was a valid heart valve substitute(17-20). Carpentier et al.(21) suggested that variations in histologic structure and durability resulted in part from inadequate preservation of the valve during the shipping process and large variations in the intervals between harvesting and glutaraldehyde treatment and in part too from high-pressure glutaraldehyde fixation. These authors expressed the hope that reduction of turbulence by the supra-annular concept and improved preservation of the valve would minimize the incidence of calcification.

In view of the low incidence of thrombo-embolic events in patients with tissue valves, it is surprising that there are reports of massive thrombosis in relation to Carpentier-Edwards prostheses(2,22). Phillips et al.(23) described subvalvular thrombotic obstruction of an aortic porcine xenograft. The thrombus appeared to have arisen at the junction of the aortic and mitral valve annuli. Bornstein and Sandroni(24) reported a patient in whom left atrial thrombosis

occurred after mitral valve replacement with an unspecified type of glutaraldehyde-treated bioprosthesis. In our patient(2),the thrombosis involved the aortic valve prosthesis,but spared an identical type of prosthesis in the mitral position. The patient with uninfected prosthetic valve thrombus described by Cohen et al.(22) also involved an aortic valve prosthesis.

Angell and Angell(35), while reviewing porcine xenograft heart valves, commented upon an apparent trend for current porcine valves to undergo sterile valvular degeneration at 5-7 years post-implantation. Many of the degenerative changes are related to host reactivity e.g., calcium deposition and host phagocytic activity. Because of similarities in the manufacturing process and complications of Hancock and Carpentier-Edwards xenograft prosthetic valves, several reports do not separate their results regarding groups of patients including both types of prostheses(36-43). Hatcher et al.(38) reported that the highest incidence of tissue failure occurred in young patients after six years of implantation. Their data suggest that use of the valve should be restricted to older patients in whom anticoagulation is contraindicated. In their report dealing with the long-term failure rate and morphological correlations in porcine valvular bioprostheses, Schoen et al.(44) noted that causes of valve failure included calcification-related cuspidal tears, tears without calcium deposits, cuspidal stiffening without any tears, but with calcium deposits and thrombosis. Late primary dysfunction was most often due to degenerative processes, especially calcification, often with secondary tears. However, cuspidal tears (without associated calcification or thrombosis) predominated at shorter intervals.

Several papers give an overall view of the subject of porcine bioprosthetic heart valve replacement(45-49). Geha et al.(39,50) and Magilligan et al.(51) noted a high incidence of early failure of porcine xenograft heart valves in children and young adults, but excellent medium and long-term results

in older adults, in whom severe dysfunction occurred mainly with recurrent infective endocarditis. Thromboembolism occurred only in patients with mitral valve replacement, especially in those with atrial fibrillation and if no anticoagulation was given. Sarabu and Parker(52) have recorded an unusual functional abnormality of a porcine xenograft cardiac valve that may be difficult for a pathologist to detect on morphological examination alone. Two of their patients required re-operation because in each patient it was discovered that one of the cusps of the mitral prosthesis was in the fixed-open position with no evidence of a peri-valvular leak. These authors assumed that the failure of the leaflet to close properly had been present from the operation.

Structural alterations in porcine xenografts described by Ashraf and Bloor(53) included fibrin deposits, erythrocyte trapping, disruption of the valve matrix, and interstitial oedema 2 years and 2 months after implantation. Scanning electron microscopy demonstrated an absence of endothelial cells. Camilleri et al.(54) observed no significant evidence of tissue rejection in 29 xenograft bioprostheses which had been implanted for periods of up to 115 months. They emphasized three factors : (i) disruption of the endothelial cell barrier and lack of significant host endothelialization ; (ii) increased cuspidal permeability, which favours calcification and lipid accumulation ; (iii) biodegradation of the collagen framework. Contrary to this experience with commercially available bioprostheses, Bodnar et al.(55) stated that porcine aortic valves may be processed in glutaraldehyde without loss of integrity of the endothelium and with the development of optimal collagen fibre structure. However, their valves were evaluated after only up to 6 months experimental implantation and their illustrations did not demonstrate endothelial cell persistence. The findings in my patients with Carpentier-Edwards prostheses mirrors the experience of Ashraf and Bloor(53).

Ishihara et al.(1) classified and described the structure

of cuspidal tears and perforations in porcine bioprosthetic cardiac valves implanted in patients. Such lesions were more frequent in the left and non-coronary cusps, than in the right coronary cusp (which in the prostheses studied had a muscular shelf at its base). These authors concluded that cuspidal tears and perforations develope in bioprostheses as a result of structural failure of the connective tissue components. Types I, III and IV tears/perforations were observed in some of the bioprostheses of patients in my study. Early leaflet perforation as a cause of bioprosthetic dysfunction has also been described by Nunez et al.(56). In two of their patients, the cut ends of the sutures used for valve insertion were believed to be the cause of the cuspidal perforations. This situation may be prevented by inserting the sutures in the periphery of the sewing ring and cutting the sutures flush with the knots. Their third case showed massive collagen breakdown due to inadequate collagen fixation by the glutaraldehyde treatment. Torn xenograft leaflets may produce unusual auscultatory findings(57,58). A high-resolution method of spectral analysis ("maximum entropy method"), which has been used to study aortic porcine valve closing sounds, may be useful for the detection of intrinsic xenograft dysfunction(58).

Experimental evidence(59) indicates that glutaraldehyde preserved porcine heart valves are vulnerable to compressive flexure, which produces fatigue-induced damage and this may limit long-term durability. Degenerative changes are more severe in the mitral than in the aortic valve position(60). This is probably related to the greater closing pressure that the mitral valve is subjected to. Spontaneous xenograft failure usually occurs in a progressive and gradual fashion, but occasionally acute, catastrophic, spontaneous xenograft failure has been encountered(61). Biodegradation of collagen is the commonest cause of failure, but occasionally manufacturing faults may be responsible e.g., the case of Grehl et al.(62) in which 2 leaflets of a Carpentier-Edwards

porcine xenograft valve tore away from the aortic wall. This probably resulted from thinning of the aortic wall beyond a critical point of maintenance of wall strength during the process of mounting the xenograft on the stent.

CHAPTER 12.

CALCIFICATION OF GLUTARALDEHYDE-PRESERVED PORCINE XENOGRAFT VALVES IN YOUNG PATIENTS

CHAPTER 12.

CALCIFICATION OF GLUTARALDEHYDE-PRESERVED PORCINE XENOGRAFTS IN YOUNG PATIENTS

It is estimated that stent-mounted glutaraldehyde preserved porcine aortic valves (GPVs) have been used in over 500,000 cardiac valve replacements since 1971(1-12,53). Late calcific degeneration of GPV occurs commonly in long-term valve replacements and often results in bioprosthetic failure(3-18). One of the earliest reports of calcification of a glutaraldehyde-preserved porcine xenograft came from Cape Town(19). There are numerous isolated case reports of valve dysfunction resulting from calcification(20-24) and several larger studies reveal that calcification may be more common in the younger age group(8-12,26-29). At Groote Schuur Hospital between 1975-1980, 670 glutaraldehyde-preserved porcine xenografts have been inserted in 568 patients in the aortic and mitral positions(30). Of these, 81 were Hancock and 589 were Carpentier-Edwards prostheses. Fifty-four of the Groote Schuur Hospital patients were under 16 years of age at the time of implantation. Seven of these patients have required re-operation to replace nine prostheses (7 mitral and 2 aortic) for calcification and severe stenosis. In addition, another young patient had a xenograft inserted elsewhere and presented with severe stenosis. A further 3 young patients died and postmortem revealed severely calcified, stenotic prostheses. The latter 3 patients have been included in Chapters 10 (Hancock prosthesis) and 11 (Carpentier-Edwards prosthesis) and one of these cases has been published previously(19).

CLINICAL FEATURES

The clinical features at the time of presentation, catheterization findings, and outcome in the 11 patients are listed in Table 12.1. All patients were 16 years of age or younger at the time of initial operation (mean age 13 years,S.D.= 1.5). There were 6 girls and 5 boys ; all had been operated upon for rheumatic valvular disease with remission of symptoms post-operatively. Seven patients had isolated mitral valve replacement, 3 had combined aortic and mitral valve replacement, and one patient had isolated aortic valve replacement. There were 12 Carpentier-Edwards prostheses and 2 Hancock prostheses. All of the 11 patients presented with prosthetic malfunction less than 33 months after the initial operation (range 12 to 33 months, mean 22 months). Two patients (numbers 8 and 10) died suddenly and unexpectedly. Both showed heavily calcified and stenosed xenografts at autopsy. One patient (number 9) presented with sudden pulmonary oedema and died before re-operation could be performed. Autopsy again revealed severely calcified xenograft leaflets(19). One patient (number 3) presented with syncope and increasing dyspnoea. The remaining 7 patients (numbers 1, 2, 4, 5, 6, 7 and 11) all had a relatively short history of symptoms of dyspnoea or had severe pulmonary oedema when first seen. One of these patients (number 2) was operated upon twice, once for a disrupted, calcified mitral prosthesis and a second time 11 months later for disruption and calcification of the aortic prosthesis. At operation in all cases the prosthesis was heavily calcified and stenosed.

Seven of the 8 patients who underwent replacement of the calcified xenografts are alive and well following re-operation. One patient (number 11) died 3 months after his second operation. Poor left ventricular function had been demonstrated at cardiac catheterization prior to operation. Before the clinicians became aware of the extent of the problem of xenograft calcification in young persons, a few of

the early patients unfortunately had a second xenograft inserted.

TABLE 12.1 PRESSURE GRADIENT BEFORE REOPERATION AND OUTCOME IN PATIENTS WITH CALCIFIED XENOGRAFTS

PT. NO.	AGE AT 1st OP.	VALVE, SITE, SIZE	TIME TO RE-OP (months)	PRESS. GRAD(mmHg)	PROSTHETIC AREA(cm2)	OUTCOME
1	14	M,CE27	21	26	0.3	A & W
2	13	M,CE29 A,CE23	16	63	0.5	A & W
3	12	M,CE27	27	27	1.0	A & W
4	11	M,H27	33	25	0.6	A & W
5	12	M,CE33	23	20	0.5	A & W
6	12	M,CE27	23	18	0.7	A & W
7	15	M,CE29	24	16	1.0	A & W
8	14	M,CE27 A,CE21	*	--	--	DIED
9	14	M,H29	**	--	--	DIED
10	16	A,CE23	***	--	--	DIED
11	13	M,CE29 A,CE21	20	12	0.5	DIED

CE=Carpentier-Edwards. H=Hancock. A & W=Alive and well after re-operation.M=Mitral,A=Aortic,Press.Grad.=Mean Pressure Gradient,M.V.A.=Mean Valve Orifice Area,Re-op.=Re-operation, PT.=Patient.Survival after first op.(mths):*=14;**=12;***=19.

PATHOLOGY

Pathological examination of the calcified xenografts (3 obtained at autopsy and the rest as surgical specimens) revealed essentially similar features in each. By way of avoiding repetition, the pathological changes observed will be described together and differences between individual cases will be mentioned.

Calcification (Figures 12.1 - 12.4) involved all 3 cusps in each xenograft. In most instances the calcified area was enclosed by a superficial layer of non-calcified cuspidal tissue (Figure 12.3). The zones of the cusp undergoing calcification showed well-preserved collagen and the ghost outlines of pre-existing cuspidal fibroblasts. Calcification mostly spared the portions of the cusps near the free margins. In a few areas, especially near the commissures, the calcification was present as calcified excrescences, which deformed the otherwise smooth cusp surface. Calcified areas still stained positively with the von Kossa and alizarin red stains after mild decalcification prior to routine tissue processing. Calcified zones also stained positively with empirical histological stains for fibrin (Martius scarlet blue and picro-Mallory methods). However, immunoperoxidase staining of the sections for fibrinogen often revealed scanty fibrin thrombus on the outflow portion of the cusps, but the calcified zones as well as the remainder of the cuspidal substance were negative for fibrinogen. The results with the empiric stains are interpreted as non-specific, false-positive staining. Stains for micro-organisms were uniformly negative.

One prosthesis showed additional calcification of myocardial fibres in the base of a cusp ; in another prosthesis two of the calcified cusps were torn. Only one prosthesis exhibited an histiocytic and foreign body giant cell reaction to the xenograft cusps. The cellular aggregation appeared unrelated to the cuspidal calcification. Light

microscopy of the xenograft valves revealed an appearance of dystrophic cuspidal calcification in a patchy, unpredicatable fashion. Apart from the calcification, the xenografts appeared no different from other xenografts that I have examined at various periods after implantation.

Electron microscopy was performed upon 7 of the xenografts. The tissue examined was taken from macroscopically non-calcified portions of the xenograft valves. Ultrastructural evidence of very early calcification was observed in 3 of the seven valves. In 2 of the three valves the earliest sign of calcification was observed in the interstitium (Figure 12.4) adjacent to collagen fibres and fibroblast-like cells. One valve had very early calcification within the cytoplasm of a fibroblast-like cell.

Figure 12.1 : Left atrial view of the severely calcified, stenotic Hancock bioprosthesis of case 9. Left atrial thrombus is present.

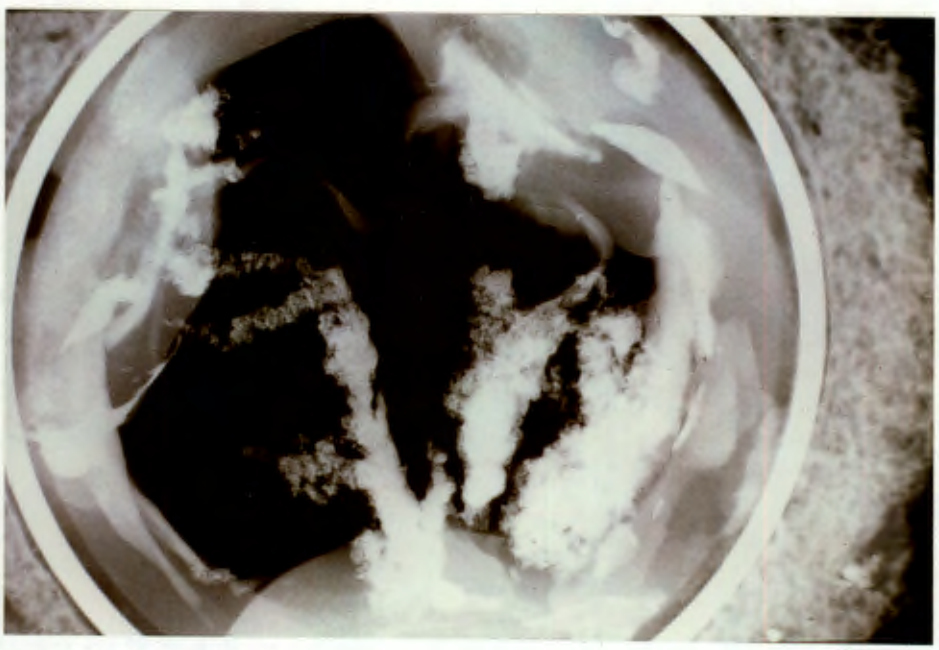

Figure 12.2 : Radiograph of a surgically excised calcified Hancock valve. Calcification is present in all 3 cusps. The prosthesis has a narrow, wire-like base ring.

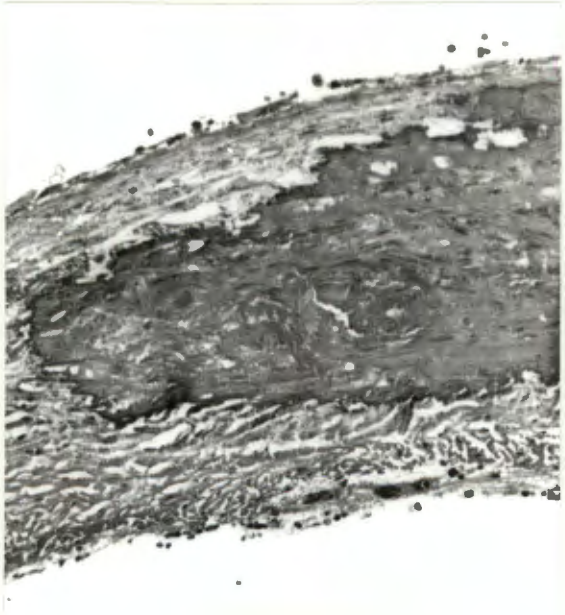

Figure 12.3 : Histological section of a cusp of the calcified Hancock valve shown in Figure 12.1 shows calcification to involve the core of the cusp with sparing of the superficial portions of the cusp. (Haematoxylin-eosin, X 150).

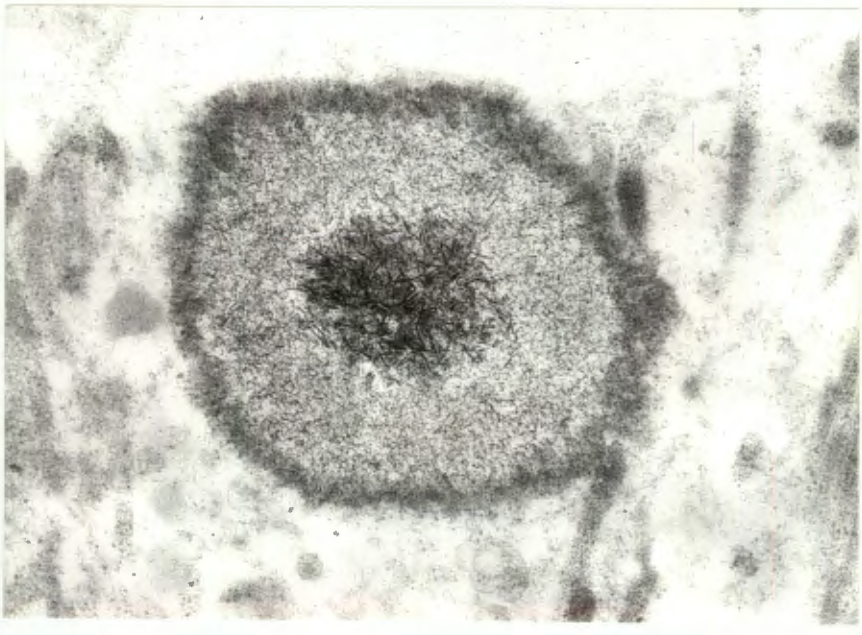

Figure 12.4 : Early calcification within Hancock cuspidal interstitial tissue is seen as a central, densely stained nidus within an aggregate of hydroxyapatite crystals. (Uranyl acetate and lead citrate, X 45000).

COMMENT

The significant feature of the calcification in these cases is that it occurred in patients under the age of 16 years. A total of 54 patients less than 16 years of age who have had xenografts inserted for chronic rheumatic heart disease was followed up at Groote Schuur Hospital(30). Of these, 7 developed severe stenosis requiring re-operation and 3 patients died. During the same period of follow-up no calcification causing valve dysfunction was observed in any of the 514 patients over the age of 16 years with similar prostheses. Others have reported a similar experience(8,26,27). Calcification of xenografts in adults has sometimes been reported(27-29) and more recently a few such cases have been encountered at our institution.

The reason for the discrepancy between the two age groups is not clear, as all of our patients had been managed similarly and all had received the usual anticoagulation regimen. None had evidence of infective endocarditis or of an abnormal calcium metabolism, although all had an elevated alkaline phosphatase level in keeping with their age. Most of the earlier reports of calcification have been in patients with Hancock prostheses. At our institution, the Carpentier-Edwards prosthesis has been more frequently implanted. It is not surprising that a similar pattern of calcification may involve this prosthesis, as there are only minor differences in preparation between the two valves.

In addition to the age distribution, another unusual feature is the fact that the calcification mainly involves the central core of the cusps and often spares the superficial portions. Although calcification is a common complication of aortic valve homografts(31,32), it was not a significant complication of formaldehyde-treated porcine xenografts(33). The limited durability of the latter prostheses may also have

played a role in the lack of calcification, since most failed early and thus may not have been left in situ long enough for calcification to occur. A variety of possible reasons for calcification of glutaraldehyde-preserved porcine xenografts has been proposed, including the different calcium metabolism of young persons(26), infection of the xenograft(34), the presence within the cusp of a calcium-binding amino acid(9), and the repeated flexing of the cusps(35). Glutaraldehyde is a notoriously poorly penetrating fixative(30). Cross-linking of the surface layers makes it progressively harder for glutaraldehyde to penetrate the tissue bulk in conventional reactions carried out at pH 7 and this can lead to incomplete fixation of the tissue(36). The superficial zones of the cusps, which are usually free of calcification, are the sites of the cusp that are fixed earliest and best by the glutaraldehyde solution. It is theoretically possible that alterations favouring subsequent calcification may develop in the core of the xenograft cusps in the period between valve excision and penetration of glutaraldehyde into the centre of the cusps. More recently, for sterilization purposes, the Carpentier-Edwards prostheses have been treated with formaldehyde during their manufacture(37). It is uncertain whether such treatment will have any effect on the propensity of these prostheses to calcify.

It is apparent from our data and other reports in the literature(8,9,13,17,26,27,38-47) that glutaraldehyde preserved porcine xenografts are not suitable for insertion in children and adolescents. In addition to the Hancock and Carpentier-Edwards prostheses, other glutaraldehyde-preserved porcine aortic valve prostheses e.g., the Angell-Shiley bioprosthesis appear to suffer from a similar problem of calcification in young hosts(48). Bovine pericardial prosthetic valves develop calcific obstruction significantly earlier than do the porcine valves(39). It is likely that all young persons with glutaraldehyde-treated bioprostheses will require early re-operation because of calcification. The

policy at Groote Schuur Hospital(30) is to follow all these young patients at 3 monthly intervals and to perform cardiac catheterization if they exhibit any symptoms of reduced effort tolerance, auscultatory features of prosthetic stenosis or pulmonary hypertension, electrocardiographic signs of progressive rightward axis deviation, or radiological evidence of pulmonary congestion. The cause of the bioprosthetic cuspidal calcification observed in young persons still awaits final elucidation.

Experimental models in animals will hopefully provide more information in this regard(49-52). Levy et al.(53) found in a study of subcutaneous implants of GPVs in rats that glutaraldehyde fixation of porcine aortic leaflets was a prerequisite for the calcification of GPV implants. These authors point out that while the specific steps in the glutaraldehyde treatment that promote the calcification are not known, the specific types of cross-links formed may be responsible. The pyridinium cross-link, which is one of the major types of glutaraldehyde induced cross-links(54-56) is directly analogous to similar compounds found in bone derived collagen and the desmosine residues of elastin(53). The pyridinium cross-link is a quartenary amine and could theoretically cause an influx of phosphate into the inter-fibrillary spaces of the collagen helices possibly leading to hydroxy-apatite nucleation. Structural proteins rich in native cross-links, such as elastin or collagen, may promote calcification solely on the basis of the extent of cross-linking(53). New observations portray calcification processes as similar whether occurring normally or pathologically(57). Most forms of calcification are initiated by membranous organelles, i.e. extra-cellular, calcifying "matrix vesicles" or intra-cellular mitochondria. Matrix vesicles promote calcification through calcium-binding phospholipids and phosphatase activity. Mitochondria use a forceful, inwardly directed calcium and phosphate transport mechanism. After mineral initiation, the proliferation of

mineral crystals is dependent on regulatory factors such as extra-cellular calcium and phosphate and other mineral inhibitors and promoters.

The unsolved problem for the manufacturers of xenograft bioprostheses is how such calcification may be prevented on a long-term basis. Most chemical methods used to date in the preparation procedure of GPVs have included materials to prevent precipitation or to compete with calcium for active sites. Most of these approaches show good short-term results which diminish as the anti-calcific agent leaches from the tissues(21). Others have attempted to use adsorbed sodium dodecyl sulphate(50), surfactant, sodium borohydride(58), special buffers or infiltration of the tissue matrix by natural or synthetic polyelectrolytes.

Porcine mitral valve calcification has been identified as a cause of intra-vascular haemolysis in children and the presence of haemolysis may be taken as an indication of such dysfunction(46). It has been suggested that some systemic emboli in porcine valve recipients may not be due to intra-cardiac or prosthetic thrombosis, but to detachment and migration of fragments of degenerative, calcified xenograft cuspidal tissue(29,59).

CHAPTER 13.

PATHOLOGY OF CARDIAC VALVE REPLACEMENT WITH MISCELLANEOUS TISSUE VALVES

CHAPTER 13.

PATHOLOGY OF CARDIAC VALVE REPLACEMENT WITH MISCELLANEOUS TISSUE VALVES.

1. AUTOLOGOUS FASCIA LATA HEART VALVE PROSTHESIS

Only one patient with such a prosthesis was encountered, a 17-year-old coloured female, who had undergone a previous mitral valvotomy for chronic rheumatic valvular heart disease (mitral stenosis). Her mitral valve was replaced by an autologous fascia lata prosthesis. She remained well for 8 months. Two weeks before her death she was admitted to Groote Schuur Hospital because of a skin rash and congestive cardiac failure. The latter was thought to be due to infective endocarditis and, although no organisms were cultured, she was given Penicillin and Gentamycin. The drug rash was attributed to Lasix, which was stopped, but she died soon afterwards.

At autopsy her heart weighed 680 grams and showed generalized hypertrophy and chamber dilatation. Infected vegetations were present on the fascia lata prosthesis and one of the cusps had torn, rendering the valve severely incompetent. Histologically the vegetations contained Gram-positive cocci. The aortic valve showed early aortic stenosis. Healed infarcts were present in the kidneys, the lungs showed a bronchiolitis, and the skin showed features of an allergic vasculitis.

References for the fascia lata valve prosthesis are given in Chapter 2 (references 179 to 234 inclusive).

2. IONESCU-SHILEY BOVINE PERICARDIAL XENOGRAFT HEART VALVE PROSTHESIS

I have had three hearts containing Ionescu-Shiley pericardial xenograft prostheses referred to me for examination. All three patients had chronic rheumatic valvular

heart disease and all three had undergone heart valve replacement at another institution.

CASE 1

This 23-year-old coloured female had severe stenosis plus incompetence of both her aortic and mitral valves. Her mitral valve was replaced by a 27 mm diameter Hancock prosthesis and the aortic valve was replaced by a 23 mm diameter Ionescu-Shiley bioprosthesis ; her aortic root was widened using a Gortex sheet. Despite repeated attempts, she could not be weaned off the heart-lung machine. Autopsy revealed that the Ionescu-Shiley bioprosthesis had been positioned in such a way that the prosthesis produced significant obstruction of both of the coronary arterial ostia. Grade 4 (75%+) luminal narrowing by atherosclerosis was noted in the right coronary artery and in a diagonal branch of the left anterior descending coronary artery. Histology of the left ventricle revealed healed sub-endocardial infarction plus recent contraction band necrosis (myofibrillar degeneration / coagulative myocytolysis). Numerous Aschoff bodies were present in the myocardium. The patient's death appeared to be due to a deficiency in operative technique.

CASE 2

This 48-year-old white female had suffered from mitral stenosis and incompetence for 18 years. Three years before her death she had undergone a mitral valvotomy. On 23rd December,1981 her mitral valve was replaced by a 27 mm Ionescu-Shiley bioprosthesis and the aortic valve by a 21 mm Bjork-Shiley prosthesis and a tricuspid annuloplasty was also performed. However, intra-operative air embolism occurred, resulting in permanent brain death. The ventilator was switched off on the morning of the third post-operative day.

Morphological examination of the 492 gram heart revealed

mild subaortic obstruction produced by the Ionescu-Shiley mitral prosthesis. One of the sewing ring sutures of the latter prosthesis was looped around one of the commissural posts (Fig. 13.1). This led to tethering down of the 2 cusps which were attached to this post, with the production of minimal to mild valvular incompetence and possibly some stenosis. The supporting post at this site indented the septal endomyocardium. The Bjork-Shiley prosthesis showed no intrinsic abnormality, but the disc appeared to impinge against the aortic wall in the fully open position. The latter is difficult to assess in the formalin-fixed state and may be a fixation artefact. Scanty thrombus was present on the tricuspid annuloplasty sutures. The latter appeared to be unusually long and hanged down into the right ventricle. The left atrium contained fresh and organized thrombi. The right lower pulmonary vein was thrombosed. Grade 4 (75%+) atherosclerotic luminal narrowing was observed in the 2 major branches of the left coronary artery and the right coronary artery showed an old complete occlusion.

Histology of the left ventricle showed focal coagulative necrosis,which was evoking an early neutrophile response. Some of the small coronary arteries were thick-walled and one contained a thrombo-embolus. The Ionescu-Shiley prosthesis showed no significant microscopical abnormality. Operative air embolism was the principal cause of death.

CASE 3

This 14-year-old black female with chronic heart failure due to mitral incompetence and aortic stenosis, had her mitral valve replaced by a 25 mm Ionescu-Shiley bioprosthesis and the aortic valve was replaced by a 19 mmm St Jude Medical prosthesis. The patient was weaned off the heart-lung machine with difficulty at the end of the operation and survived 4 hours with a low blood pressure. The prostheses appeared normal naked eye and the Ionescu-Shiley valve cusps showed no

abnormality histologically. The left ventricle showed widespread contraction band necrosis, raising the possibility of inadequate intra-operative myocardial protection. Some small coronary arteries contained recent thrombo-emboli, but it is uncertain as to whether there is any relationship between the emboli and the myocardial damage.

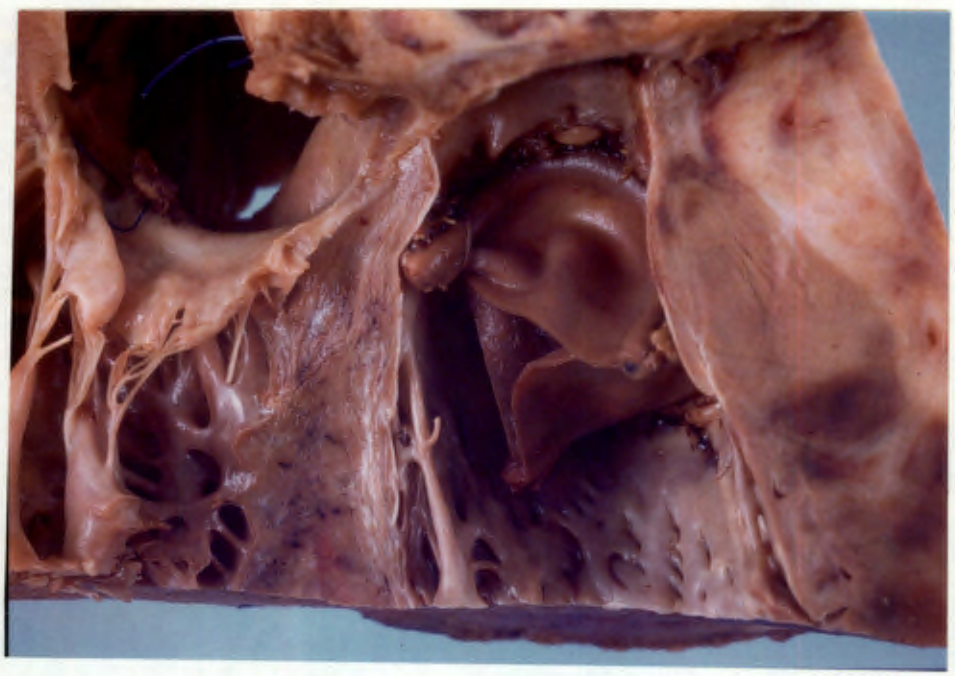

Figure 13.1 : Ionescu-Shiley mitral bioprosthesis of patient 2 has a sewing ring suture looped around the supporting post, which is indenting the inter-ventricular septal endocardium. The suture has slightly reduced the amount of free margin of the 2 cusps attached at this site.

3. EXPERIMENTALLY IMPLANTED IONESCU-SHILEY BIOPROSTHESES

Four Ionescu-Shiley bioprostheses were implanted into 4 Chacma baboons as controls for similarly implanted Mitroflow Medical bioprostheses. Results are given in Chapter 16.

COMMENT

There are too few patients with Ionescu-Shiley bioprostheses in the present study for any conclusions to be drawn regarding the efficacy of this valve substitute. Several published reports attest to its durability and low thromboembolic rate(1-6). However, others have reported complications with this prosthesis e.g., accelerated cuspidal calcification(7-9), collagenous overgrowth(10) and cuspidal disruption(11,12). Thubrikar et al.(13) have analysed the design and dynamics of various aortic bioprostheses in vivo. The configurations in the radial direction indicated that Carpentier-Edwards and Hancock valves have leaflets that are cylindrical, whereas the leaflets of Ionescu-Shiley valves are roughly spherical. Ishihara et al.(14) examined the structure of bovine parietal pericardium and of unimplanted Ionescu-Shiley pericardial valvular bioprostheses. They found that pericardial bioprosthetic cusps differ from normal pericardium by being denuded of mesothelium, but they have normal degrees of waviness in their collagen. In Ionescu-Shiley valves, the inflow and outflow surfaces of each cusp correspond to the epipericardial and serosal surfaces of parietal pericardium, respectively. The inflow surfaces have a coarse texture, chraracterized by large bundles of collagen, and the outflow surfaces have numerous grooves, which probably result from pressure exerted on the cuspidal surfaces by cotton material either during manufacture or packing of the valves.

VARIOUS PROSTHETIC HEART VALVES

CHAPTER 14.

PATHOLOGY OF CARDIAC VALVE REPLACEMENT WITH MORE THAN ONE TYPE OF PROSTHESIS IN EACH HEART

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PATHOLOGY OF CARDIAC VALVE REPLACEMENT WITH MORE THAN ONE TYPE OF PROSTHESIS IN EACH HEART

The 24 patients studied had 52 prostheses of various types implanted, i.e., each heart contained more than one kind of prosthetic heart valve (see Tables 14.1 and 14.2). The aetiology of the native heart valve disease in these patients was as follows : rheumatic heart disease 21, primary infective endocarditis (normal pre-existing valves) 2, and congenital heart disease 1.

GROUP 1

The 14 patients in this group had a mean age of 35 years (S.D.= 14) and a range of from 18 to 63 years. There were 9 whites and 5 coloureds ; eight were females and 6 were males. Eleven patients had chronic rheumatic-type deformities of their native heart valves prior to surgery, 2 had infective endocarditis and one patient had congenital heart disease (mitral stenosis, double outlet right ventricle, ventricular septal defect and aortic incompetence). Their mean survival period was 4 days (S.D.= 7) with a range of 0-24 days. The mean heart weight was 682 grams (S.D.= 229) with a range of from 420-1172 grams. Only one out of the 31 prostheses implanted in the group 1 patients showed evidence of thrombus deposition at postmortem. This was observed on the sewing ring and on the cage of a Starr-Edwards prosthesis which had been implanted for 5 days. The Bjork-Shiley aortic valve prosthesis in the same patient was free of thrombus. The 14 patients were observed to have the following organ infarcts : heart 2, lung 1, spleen 1, kidney 1, and limb 1. However, as 9 out of the 14 patients had only partial postmortems performed and the heart only was referred to me from elsewhere for examination, the incidence of infarction may be underestimated in this

group. In the majority of these patients I was able to obtain only a verbal report regarding the presence or absence of organ infarcts at autopsy. Table 14.3 lists the principal causes of death in the group 1 and group 2 patients.

TABLE 14.1 : TYPES OF PROSTHETIC VALVES IMPLANTED IN 24 PATIENTS WITH MORE THAN ONE KIND OF PROSTHESIS IN EACH HEART

SITE	GROUP	UCT	LILL	B-S	SJM	HAN	S-E	C-E	I-S	TOTALS
AV	1	4	1	4	2	0	0	0	1	13
AV	2	3	1	6	0	0	0	0	0	10
AV	TOTAL	7	2	10	2	0	0	0	1	22
MV	1	0	1	1	2	1	7	2	0	14
MV	2	1	1	0	0	0	6	1	1	10
MV	TOTAL	1	2	1	2	1	13	3	1	24
TV	1	0	1	0	1	0	1	1	0	3
TV	2	0	0	0	0	0	1	0	0	1
TV	TOTAL	0	1	0	1	0	2	1	0	5
PV	1	0	0	0	0	1	0	0	0	1
PV	2	0	0	0	0	0	0	0	0	0
PV	TOTAL	0	0	0	0	1	0	0	0	1
TOTALS		8	5	11	5	2	15	4	2	

GRAND TOTAL = 52

Code for types of prostheses: UCT=University of Cape Town, LILL=Lillehei,B-S=Bjork-Shiley,SJM=St Jude Medical, HAN=Hancock,S-E=Starr-Edwards,C-E=Carpentier-Edwards, I-S=Ionescu-Shiley.AV=aortic valve,MV=mitral valve, TV=tricuspid valve, PV=pulmonary valve.

TABLE 14.2 : COMBINATIONS OF THE DIFFERENT TYPES OF VALVES INSERTED IN 24 PATIENTS

	AV	MV	TV	PV	No.of Patients
GROUP 1					
	SJM	SJM	C-E	--	1
	UCT	SJM	SJM	--	1
	B-S	C-E	--	--	1
	I-S	C-E	--	--	1
	B-S	S-E	--	--	2
	UCT	S-E	S-E	--	1
	UCT	S-E	--	--	2
	LILL	S-E	--	--	1
	SJM	LILL	--	--	1
	B-S	HAN	--	--	1
	--	S-E	LILL	--	1
	B-S	B-S	--	HAN	1
GROUP 2					
	B-S	I-S	--	--	1
	--	UCT	S-E	--	1
	UCT	S-E	--	--	2
	B-S	S-E	--	--	4
	UCT	LILL	--	--	1
	LILL	C-E	--	--	1

Same code for abbreviations as used in Table 14.1.

GROUP 2

The 10 patients who survived longer than 30 days post-operatively had a mean age of 34 years (S.D.= 17) and a range of 14-57 years. There were 5 whites, 3 blacks and 2 coloured patients. Six of the patients were females. Mean post-operative survival period was 355 days (S.D.= 341) with a range of 34-1147 days. The mean heart weight was 873 grams (S.D.= 192) with a range of from 492-1138 grams. Eight out of the 22 prostheses present in the ten group 2 patients bore bland antemortem thrombi. One U.C.T. prosthesis had abundant thrombi on the bobbin and sewing ring, 4 Starr-Edwards mitral prostheses had moderate amounts of thrombus on the cage struts near to or at the apex, 2 Bjork-Shiley aortic valve prostheses had scanty sewing ring thrombi and 1 Lillehei mitral prosthesis was extensively covered on both aspects by thrombus which severely narrowed the major orifice and totally occluded the lesser orifice.The following organ infarcts were observed in these 10 patients : kidneys 3, brain 3, spleen 2, heart 2, and lung 1. Only 2 out of the 10 patients were partial postmortems. For lists of the principal causes of death and non-fatal complications in these patients please see Tables 14.3 and 14.4.

TABLE 14.3 : PRINCIPAL CAUSES OF DEATH (1 PER PATIENT) IN 24 PATIENTS WITH VARIOUS TYPES OF IMPLANTED PROSTHESES

GROUP 1	
UNKNOWN	4
PROSTHETIC DISPROPORTION	1
OBSTRUCTED CORONARY OSTIA	1
STONE HEART	2
BLEEDING	2
MYOCARDIAL FAILURE	1
THROMBOEMBOLISM	1
INFECTED PROSTHESIS	1
PULMONARY HYPERTENSION	1
GROUP 2	
MYOCARDIAL FAILURE	3
INFECTED PROSTHESIS	2
THROMBOEMBOLISM	2
THROMBOSED PROSTHESIS	1
RHEUMATIC PNEUMONITIS	1
AIR EMBOLISM	1

TABLE 14.4 : NON-FATAL COMPLICATIONS/ASSOCIATED CONDITIONS IN 24 PATIENTS WITH VARIOUS IMPLANTED PROSTHESES

GROUP 1	
PNEUMONIA	2
PULMONARY VALVE MARANTIC THROMBUS	1
SEVERE HAEMOLYSIS	1
GROUP 2	
75%+ CORONARY ARTERIAL NARROWING	2
PARTIAL PROSTHETIC DEHISCENCE	2
DIGITALIS TOXICITY	1

COMMENT

GROUP 1

The 4 patients with unknown cause of death may have died of early post-operative arrhythmia. Three of the patients did not survive the operation, and one lived for only 3 hours. The patient who died because of prosthetic disproportion had had pre-operative infective endocarditis of the aortic and mitral valves with aortic ring abscesses. Following excision of as much of the infected tissue as possible, there was a deficiency of aortic valve ring tissue. A patch was inserted in the aortic root and the latter plus the aortic root were angled obliquely across the summit of the Bjork-Shiley aortic valve prosthesis. The disc of the prosthesis appeared to have a limited opening motion as a result of this. A patient with an Ionescu-Shiley aortic valve prosthesis, who had both coronary ostia partially obstructed by the commissural supports of the prosthesis, did not survive the operation. Two patients with so-called 'stone heart' (see chapter 17) showed global subendocardial haemorrhagic infarction due to inadequate myocardial protection during cardiopulmonary bypass. Candida albicans was cultured bacteriologically from the infected prosthesis of the one patient with infective endocarditis.

GROUP 2

Myocardial failure was the commonest cause of death in these patients. Staphylococcus albus was cultured from the blood of both of the patients with infected prostheses in this group of patients. The patient with the thrombosed U.C.T. mitral valve prosthesis also had had a U.C.T. tricuspid prosthesis replaced surgically 2 months before because of

thrombosis. The fatal thromboembolism observed in 2 patients involved the heart and brain respectively. The patient who suffered operative cerebral air embolism lived on a respirator for 34 days with evidence of brain death before it was decided to switch off the machine. Partial prosthetic dehiscence was observed in relation to 2 Starr-Edwards mitral valve prostheses in the absence of signs of infection.

These data on patients with more than one type of implanted cardiac prosthetic valve in their heart are included here for completeness sake. Most articles dealing with prosthetic heart valves focus on one type of valve substitute only. Because of the application of a similar policy with respect to the computer programme used to maintain statistics on patients with valvular prostheses at Groote Schuur Hospital, no data are available on the yearly survival results or embolism events in this category of patient.

CHAPTER 15.

PATHOLOGY OF CARDIAC VALVULAR PROSTHESES SITUATED WITHIN TUBE GRAFTS

CHAPTER 15.

PATHOLOGY OF CARDIAC VALVULAR PROSTHESES SITUATED WITHIN TUBE GRAFTS

Nine patients were encountered who had a variety of heart valve substitutes secured within tube conduit grafts made of woven Dacron. The clinicopathological information on these patients is summarized in Table 15.1. Seven patients were whites and there was 1 coloured and 1 black patient. This autopsy group included no late survivors.

TABLE 15.1 : AUTOPSIED PATIENTS WITH VALVED CONDUIT TUBE GRAFTS

PATIENT	AGE,SEX	PRE-OP. LESION	SURVIVAL (DAYS)	PROSTHESIS	CAUSE OF DEATH
1	60,M	Ao.ANEU	0	C-E	UNKNOWN
2	2,F	TRUNCUS	0	B-S	P.HYPT.
3	39,M	Ao.ANEU	0.125	B-S	BLEEDING
4	24,F	COARCTN.	5	LILL	UNKNOWN
5	7,M	T.G.A.	9	B-S	THROMBOSIS
6	7,F	TETRALOGY	10	B-S	PATCH LEAK
7	39,M	TETRALOGY	10	C-E	C.A.STITCH
8	34,M	Ao.ANEU	20	S-E	BLEEDING
9	18,M	D.O.R.V.	24	B-S	P.HYPT.

Ao=aortic,ANEU=aneurysm,COARCTN=coarctation,M=male, F=female,TGA=transposition of the great arteries, P=pulmonary,HYPT=hypertension,DORV=double outlet right ventricle,CA=right coronary artery,C-E=Carpentier-Edwards,B-S=Bjork-Shiley,LILL=Lillehei,S-E=Starr-Edwards.

It will be observed from Table 15.1, that 3 patients were aged 7 years or less and six out of the 9 patients had their operations because of congenital heart disease. The 3 patients with acquired heart disease all had aortic aneurysms. This took the form of a dissecting aneurysm in patient 1 and saccular aneurysms of the ascending aorta in patients 3 and 8, both of whom had aortic medionecrosis. The tube graft linked the right ventricle to the main pulmonary artery in 4 patients, the right ventricle to the right pulmonary artery in 1, and the aortic root to the more distal aorta in 4 patients.

COMMENT

The 2 patients who died because of severe pulmonary hypertension, should in retrospect rather have undergone pre-operative lung biopsy prior to attempts at corrective surgery. Both deaths were attributable to errors in pre-operative diagnosis. Patient 2, who had a persistent truncus arteriosus, did not survive the operation. Autopsy revealed grade 6 pulmonary arterial lesions of the Heath-Edwards grading(1), i.e. fibrinoid necrosis of small pulmonary arteries. Patient 9 had advanced grade 3 pulmonary arterial lesions with severe luminal narrowing.

Both patients who died of bleeding suffered loss of blood from the proximal anastomosis of the tube graft to the aorta. Whilst erroneous operative technique cannot be altogether excluded, the main problem in these 2 patients was probably the delicate, friable nature of the medionecrotic aortic tissue. The cause of death was unknown in 2 patients. In patient 5 the tube graft and Bjork-Shiley prosthesis underwent thrombosis resulting in severe luminal narrowing and severe limitation of movement of the disc of the valve prosthesis.

Two patients died due to errors in operative technique. In patient 6 the Gortex patch used to seal the ventricular septal defect became partially detached as a result of several

sutures tearing free from the septal myocardium. In patient 7 surgery was made difficult by the numerous fibrous adhesions which had developed following a Brock procedure a few years before. One of the sutures securing the tube graft to the right ventriculotomy wound passed through the right coronary artery and severely narrowed its lumen.

Fiore et al.(2) compared valved and non-valved right ventricular-pulmonary arterial extra-cardiac conduits in a canine experimental model. They showed that after one year, the thickness of the neo-intimal lining was threefold greater in the valved conduits. Duran et al.(3) implanted homologous and heterologous aortic valves in prosthetic vascular tubes in experimental animals. Semb et al.(4) reported good clinical results with the use of valved xenograft conduits to correct tricuspid atresia. Nath et al.(5) discuss the radiological evaluation of composite aortic grafts used to treat aneurysm of the ascending aorta with aortic regurgitation caused by cystic medionecrosis. They found haemorrhage from the anastomotic sites to be the most important complication. (This complication was observed in 2 out of my 9 patients with external conduits and was the cause of death in 2 of the 3 patients who received conduits for acquired aortic aneurysms).

There are several clinical reports of intra-conduit obstruction due to pannus formation(6-8). Infection has also been a problem(9,10) in some cases, and so too has coronary artery compression produced by the conduit(11,12). Proper conduit placement and intra-operative recognition of possible coronary artery compression by the conduit are important in preventing significant ischaemic problems. Such fatal coronary compression is a rare complication and was only encountered in 0.35% of the 860 conduit operations performed at the Mayo Clinic(12). Porcine xenograft valves in conduits implanted in children have experienced the same problem with calcification(13,14) that was noted in valves implanted orthotopically in children. Geha et al.(13) reported a 12%

failure rate of extra-cardiac conduits, whilst Bisset et al.(15) encountered a 30% incidence of xenograft conduit failure over a shorter follow-up period. The latter authors concluded that, although valved external conduits continue to play an important role in the treatment of complex congenital heart disease, a valved conduit with greater longevity is needed for use in children.

CHAPTER 16.

EXPERIMENTAL EVALUATION OF THE MITROFLOW BOVINE PERICARDIAL HEART VALVE BIOPROSTHESIS

CHAPTER 16.

EXPERIMENTAL EVALUATION OF THE MITROFLOW BOVINE PERICARDIAL HEART VALVE BIOPROSTHESIS

INTRODUCTION

The Mitroflow pericardial heart valve (Mitral Medical International, Inc.) was conceived at a time when major problems of calcification were beginning to occur with porcine valves that had been implanted for 5 to 10 years. At that time the Ionescu-Shiley pericardial valve had demonstrated clinical success for an extended period(1). The Mitroflow bovine pericardial heart valve has undergone a series of animal tests.Attempts to develop a calf model were unsuccessful,but tests in dogs and baboons have been completed. The latter work has not yet been published. The canine animal model was tested at the University of California, Davis, California, U.S.A. as well as at St Luke's Hospital, Cleveland, Ohio, U.S.A. The primate model using the Chacma baboon was evaluated at the University of Cape Town, Cape Town, South Africa. These in vivo tests culminated in the first Mitroflow human implant in Spain on 23rd March, 1982. Each of the manufactured bioprostheses is subjected to pulsatile function testing prior to being marketed for clinical use.

STRUCTURE OF THE MITROFLOW VALVE(1)

STENT

The stent is constructed of Delrin 500, an acetal homopolymer with "low creep" properties(2). Delrin, which is a registered trademark of E.I. du Pont de Nemours & Co.(Inc.), is a highly crystalline polymer whose crystallinity is derived from the high degree of symmetry in the polymer chain. The crystallinity of Delrin is about 80% whereas polypropylene,

the other material used for some competitive stents, is of the order of 60-65%. Delrin has not only a higher and more predictable crystallinity than polypropylene, but it also has a narrower range of crystallite sizes(1). According to Mitral Medical International Inc. of Wheat Ridge, Colorado, who manufacture the valve, Delrin has a molecular structure with adequate flex and shock absorbance. Consequently, it is claimed that the stent design has the lowest profile consistent with natural leaflet action, generous leaflet coaption, no prolapse and maximum movement of the leaflets.

The stent is designed to have the maximum working orifice while having adequate structural strength at the top of the commissural posts. The shape of the scallop on the stent provides smooth action of the whole leaflet, which aims to produce optimal washing of the leaflet surfaces, combined with minimal abrasion.

SEWING RING

The sewing ring is moulded from Dow Corning medical grade silicone. Recently all the sewing rings of this prosthesis have been made to be radiopaque by loading the silicone with 40% tungsten powder. This colours the ring black, but leaves it sufficiently soft to allow the ring to adapt to the cardiac valve annulus.

STENT AND SEWING RING COVER

Medical grade Dacron fabric, manufactured by E.I. du Pont de Nemours & Co.(Inc.), covers the stent and sewing ring in such a manner so that there is a single seam and no exposed knots in order to minimize microturbulence on the valve surface and lower the chance of thrombus formation. The stent is flexible so as to reduce the closing stresses on the leaflets.

LEAFLET DESIGN

The valve leaflets are constructed from a single piece of bovine pericardium. Tissue thickness is calculated corresponding to each valve size and the larger size valves have a thicker tissue. A major design feature of the Mitroflow valve is that the tissue is mounted on the external surface of the covered stent. There are no sutures at the top of the commissure posts to reduce leaflet movement and the leaflets are able to open to essentially a full cylinder. (The bovine pericardium of the other commercially available bioprosthesis is situated inside the stent and opens as a truncated cone. This gives rise to more eddies and vortices distally). The bovine pericardium is mounted so that its inner surface (i.e., the side adjacent to the heart) forms the outflow surface of the valve to minimize the possibility of thrombus formation. This is done because during production the adipose tissue is dissected off the parietal side of the pericardium, resulting in exposure of the cut ends of the collagen fibres.

The valve is designed to have a small triangular hole at the central point of coaption which closes completely with 2-3 mm Hg of back pressure. This feature ensures synchronous leaflet action. When the valve is packaged in aqueous formaldehyde or saline,this hole may appear as a gap or as multiple gaps between the leaflets, because of the effect of the surface tension of the liquid(1). Tests have shown that total regurgitation (backflow) is insignificant(3). The manufacturers claim that the 'perfect' leaflet action of the Mitroflow valve will significantly reduce the thrombus formation on the leaflets which leads to tissue overgrowth. The latter immobilises the leaflets and may favour calcification(1). Unlike the Ionescu-Shiley prosthesis, there are no sutures tethering the leaflets at the commissures.

Careful operative technique is recommended for use of the Mitroflow valve. This includes rinsing of the prosthesis prior to implantation to prevent the aldehydes producing tissue

necrosis and para-valvular leaks. The prosthesis should also be washed frequently during the operation to protect the bioprosthetic tissue.

EXPERIMENTAL IMPLANTATION OF THE MITROFLOW PERICARDIAL VALVE(1).

The in vivo testing of the Mitroflow pericardial valve was conducted at three study centres in two different animal models :

(i) Animal Model : Canine (dogs).

The valvular replacements in dogs were carried out at 2 study centres involving two distinct surgical techniques under sterile conditions : (a) Using cardiopulmonary bypass (St Luke's Hospital, Cleveland). (b) Under profound hypothermia without cardiopulmonary bypass (University of California-Davis).

The number and duration of valvular implants is given in Table 16.1.

Table 16.1 : NUMBER AND DURATION OF VALVULAR IMPLANTS IN DOGS AT 2 STUDY CENTRES

CENTRE	POSITION	No. OF IMPLANTS & DURATION (RANGE) DAYS	
		MITROFLOW	CONTROLS
St Luke's Hospital, Ohio	MITRAL	26(1-168)	5(1-35)
Univ.California	TRICUSPID	9(27-69)	3(24-64)
Totals		35	8

(Reproduced from Monograph on Mitroflow Pericardial Heart Valve, reference 1 of this chapter).

The overall evaluation of valves implanted in the tricuspid position using profound hypothermia (University of California) suggested that the Mitroflow valves exhibit comparable morphology and histological characteristics to those of control valves(1). According to Mitral Medical Inc., the St Luke's Hospital study showed that the gross appearance of the Mitroflow and the control valves were essentially equivalent for comparable implant duration, but in some cases the Mitroflow valves were free of thrombus and had a better appearance than the control valves (Ionescu-Shiley prostheses). Both test and control valves showed similar changes in regard to leaflet integrity and extent of thrombus formation.

(ii) Animal Model : Primate (baboons)

Baboons were chosen as the second animal model since their cardiovascular and physiological systems are almost identical to those of humans. Valvular implants were carried out at the University of Cape Town,South Africa under the direction of Professor C.N.Barnard and the hearts and lungs of the sacrificed baboons were submitted to the present author for pathological examination.

Thirty-five Mitroflow valves and 4 control Ionescu-Shiley bioprostheses were implanted. The prostheses were divided into the following groups :

(i) Seven pericardial bioprostheses had been treated and manufactured by "the original pilot process", the details of which are known only to Mitral Medical Inc. All were implanted in the mitral position.

(ii) Twelve Mitroflow pericardial valvular prostheses which had been treated and manufactured by "process G", which is based on a simple glutaraldehyde fixation with no attempt

to enhance the pericardial tissue for anticalcific or antithrombogenic characteristics. All of these Mitroflow valves were implanted in the mitral position. Details of the "G" process are given in the Methods section.

(iii) Sixteen baboons received Mitroflow valves treated by "process F", which relies on tissue fixation by glutaraldehyde cross-linking of collagen molecules via the epsilon-amino groups of lysine after biological species designed to inhibit calcification have been attached through pendant carboxyl groups of aspartic and glutamic acid residues.

(iv) Nine valves comprised the "pre-human" series of Mitroflow valves which consisted of the latest model of this valve that had been developed prior to clinical trials in human patients. No details are available regarding its method of preparation. One of these valves was implanted in the tricuspid position and the remainder were placed in the mitral position.

(v) Four commercially available Ionescu-Shiley pericardial heart valves were implanted in baboons as controls. It should be noted that these valves cost about R1700.00 each. Three were placed in the mitral position and one in the tricuspid position.

Kindly see the Methods section further data regarding the methods used in this experimental study.

RESULTS

Table 16.2 lists the mean gradients across the Mitroflow valves at surgery immediately after implantation.

TABLE 16.2 : GRADIENTS ACROSS MITROFLOW VALVES AND CONTROLS AT SURGERY IMMEDIATELY AFTER IMPLANTATION

	(mm Hg +/-S.D.)
MITROFLOW VALVES	
PILOT SERIES	5.62 +/- 2.31
"G" PROCESS	6.09 +/- 1.39
"F" PROCESS	5.20 +/- 2.48
PRE-HUMAN SERIES	5.08 +/- 1.95
CONTROL VALVES	
IONESCU-SHILEY	5.33 +/- 0.15

(i) MITROFLOW VALVES PREPARED BY THE "ORIGINAL PILOT PROCESS"

The mean post-operative survival of the 7 baboons which were sacrificed at various periods following implantation of Mitroflow prosthetic valves was 81 days (S.D.= 68) with a range of from 5 to 192 days. One animal died suddenly and unexpectedly of unknown cause 1 day post-operatively. Autopsy revealed evidence of recent myocardial necrosis, the cause of which is uncertain. Pre-sacrificial cardiac catheterization of this group of primates with implanted valves revealed a mean percentage valve orifice reduction of the Mitroflow prostheses of 53.0% (S.D.= 11.5%) with a range of from 29-65%. It will be observed from Table 16.3 that 6 out of the 7 prostheses had some thrombus on the surface, and usually this was on the inflow surface of the cusps (Figs. 16.1 and 16.2). Some degree of host tissue overgrowth of the proximal portions of the cusps of the prosthesis was present in just over half of the

prostheses and a marked host immune assault with erosion of cuspidal substance was observed in only one of these valves. Only one prosthesis in this group showed attachment to the ventricular endomyocardium.

(ii) MITROFLOW VALVES PREPARED BY "PROCESS G"

The 12 baboons which received implants of the Mitroflow pericardial valves treated by "process G" were sacrificed between 100 and 380 days post-operatively, with a mean survival of 247 days (S.D.= 98.8). Pre-sacrificial cardiac catheterization revealed a mean percentage prosthetic valvular orifice reduction of 63.1% (S.D.= 11.5%) and a range of 46-73%. Ten out of the 12 valves showed thrombus deposition on the inflow surface of the cusps just proximal to the contact area (Figs. 16.1 and 16.2). Host tissue overgrowth of the cusps was seen in 11 of the 12 valves, and it was severe in 9 instances. One valve was attached to the host's endomyocardium. Another valve showed minimal cuspidal calcification which was quantitated at 5.5, 0.7 and 3.3 μg/mg per cusp respectively.

(iii) MITROFLOW VALVES PREPARED BY "PROCESS F"

The seven baboons which received implants of Mitroflow valves prepared by "process F" were sacrificed between 99 and 289 days post-operatively. Two baboons died suddenly and unexpectedly of unknown cause on days 2 and 5 post-operatively. The mean post-implantation period for the valves was 167.7 days (S.D.= 128.3). Pre-sacrificial cardiac catheterization (N=4) revealed a mean percentage prosthetic valvular orifice reduction of 38.0% (S.D.= 18.8%) with a range of 18-54%. Six of the 7 valves showed scanty or moderate thrombotic deposits on the inflow aspects of the cusps and a

severe host tissue overgrowth resulting in erosion of the original cuspidal collagen or serious shortening and distortion of the cusp was noted in 2 patients. None of the valves were attached to endocardium. One valve showed scanty, spotty cuspidal calcification and one of its cusps contained 5.5 µg calcium per mg (the other 2 cusps contained only 0.1 and 0.2 ug/mg respectively).

TABLE 16.3 : PATHOLOGY OF MITROFLOW PERICARDIAL AND CONTROL (IONESCU-SHILEY) PROSTHETIC VALVES IMPLANTED IN CHACMA BABOONS.

TYPE & NO.OF PROSTHESES	IMPLANTED (DAYS)	THROMBUS +++	++	+	0	TISSUE OVER-GROWTH (+++)	ATTACHED TO MYOCARDIUM	% V.R. (S.D.)	GRAD. (mmHg) (S.D.)
MITROFLOW, PILOT STUDY (N=7)	81	2*	2	2	1	4(1)	1	53.0 (11.5) a	13.3 (2.9) e,f,g
MITROFLOW, PROCESS "G" (N=12)	247	1	7	2	2	11(9)	1	63.1 (11.5) b,c,d	17.0 (8.2) h,i,j
MITROFLOW PROCESS "F" (N=7)	168	0	2	4	1	6(2)	0	38.0 (18.8) b	8.4 (2.6) e,h
MITROFLOW "PRE-HUMAN" (N=9)	120	1	1	5	2	4(2)	2	39.8 (23.9) c	7.6 (3.4) f,i
CONTROLS (IONESCU-SHILEY) (N=4)	128	0	1	3	0	1(1)	2	21.3 (12.6) a,d	6.3 (6.3) g,i

* INFECTED IN ONE CASE ; 0=ABSENT,+=SCANTY,++=MODERATE,+++=ABUNDANT
The differences are not significant except where indicated. p less than 0.025 =a,c,e,h,j;p less than 0.01=b,g;p less than 0.005=f,i;p less than 0.001=d.
% V.R.= percentage reduction in valve orifice area.

(iv) "PRE-HUMAN" SERIES OF MITROFLOW VALVES

There were 9 valves in this group ; 8 were implanted in the mitral position and one in the tricuspid position. The mean post-operative implantation period prior to sacrifice was 120 days (S.D.= 78) and the range was 28-220 days. The mean percentage valve area reduction was 39.8% (S.D.= 23.9%), with a range of 8-57%. Only two valves showed no thrombus on the inflow aspect (see Table 16.3). Two out of the 9 valves were rendered adherent to the left ventricular endomyocardium by organized thrombus. Two valves showed a significant host tissue overgrowth on the valve cusps.

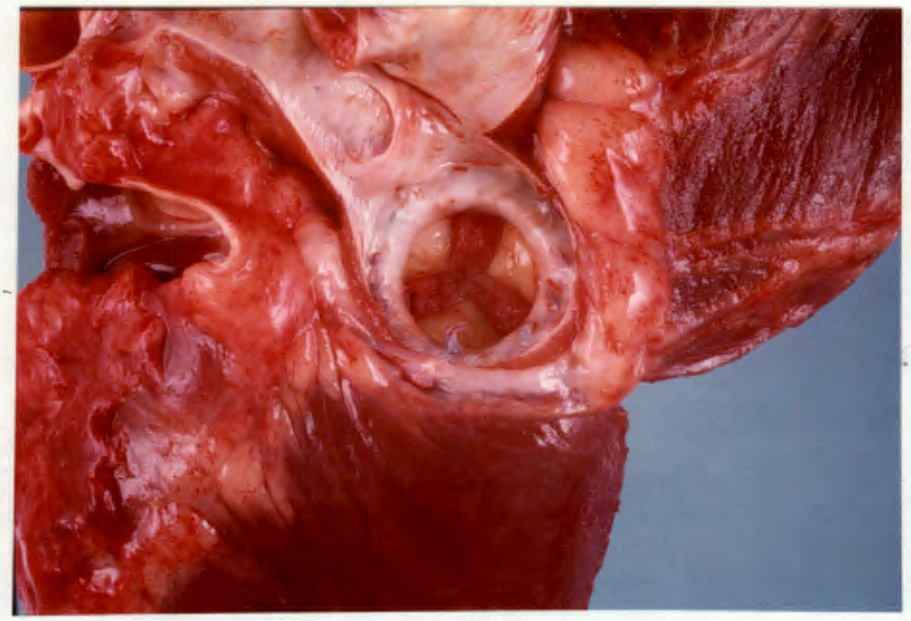

Figure 16.1 : Left atrial view of a Mitroflow valve implanted in the mitral annulus of a baboon 6.5 months prior to sacrifice. Abundant thrombus on the inflow aspect of the cusps gives a characteristic tri-radiate ("Mercedes-Benz sign") pattern of thrombus deposition. Such a pattern was commonly seen on Mitroflow valves bearing thrombi.

Figure 16.2 : Histological appearance of thrombus on convex (inflow) surface of Mitroflow valvular cusp. The acellular thrombus shows no evidence of organization. (Elastic van Gieson, X 150).

Figure 16.3 : Extensive host tissue overgrowth onto the Mitroflow valvular cusps has led to cuspidal thickening and shortening. The latter is most apparent in the cusp with thrombus on its orificial aspect.

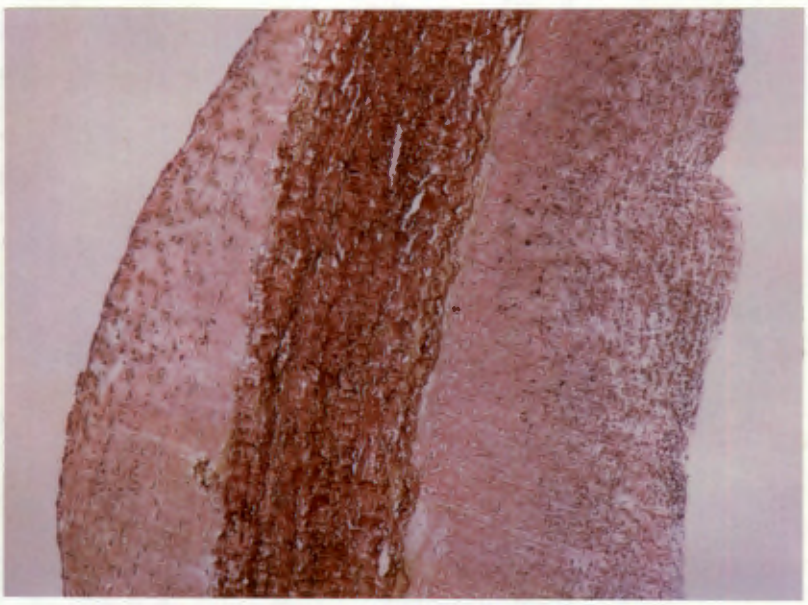

Figure 16.4 : Host tissue (myofibroblasts and collagen) has grown over both aspects of this Mitroflow valve, which had been implanted for 47 days. (Elastic van Gieson, X 150).

TRANSMISSION ELECTRON MICROSCOPY

Table 16.4 indicates the ultrastructural appearance of the state of preservation of the collagen fibres in the 5 Mitroflow valves and the one Ionescu-Shiley control valve examined by electron microscopy. The control valve (Fig. 16.5) and the Mitroflow valves all showed good preservation of their collagen fibres. However, one "pilot study" valve (Fig.12.6) showed loss of periodicity in many of its collagen fibres.

TABLE 16.4 : ULTRASTRUCTURAL ASSESSMENT OF COLLAGEN FIBRE PRESERVATION OF BOVINE PERICARDIAL BIOPROSTHESES IMPLANTED IN BABOONS

GROUP	VALVE	PERIOD INSERTED (DAYS)	STATE OF COLLAGEN PRESERVATION
MITROFLOW			
PILOT	1010	71	LOST PERIODICITY
PILOT	1417	44	GOOD
F PROCESS	1017	240	GOOD
PRE-HUMAN	1052	41	GOOD
PRE-HUMAN	1109	28	GOOD
CONTROL			
IONESCU-SHILEY	4427	31	GOOD

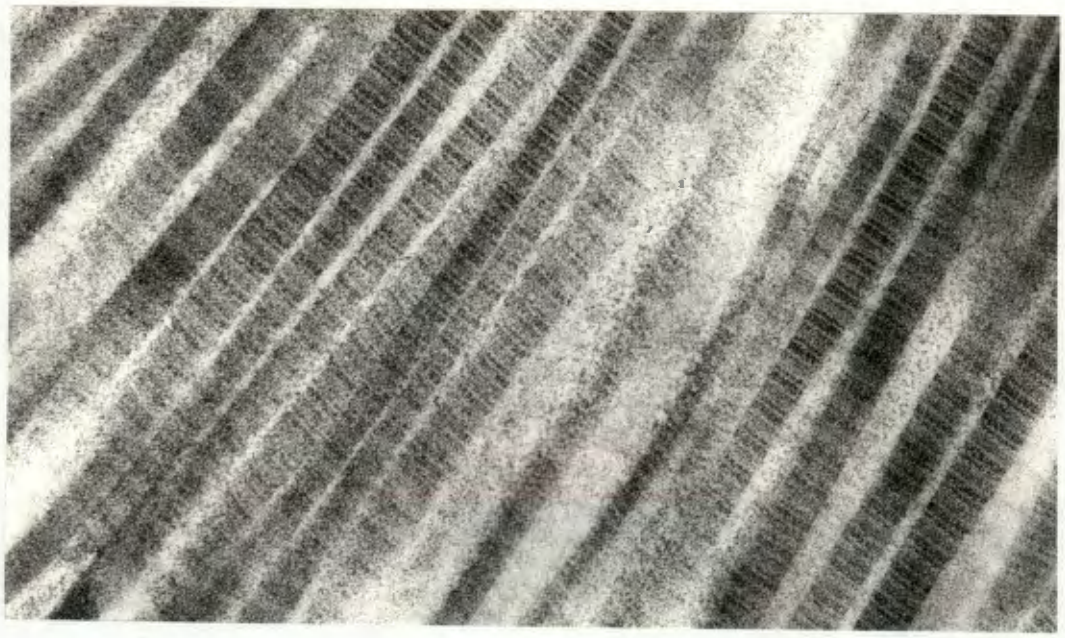

Figure 16.5 : Ultrastructural appearance of a cusp belonging to a control Ionescu-Shiley bioprosthesis 31 days after implantation. Collagen fibres still show a regular periodicity. (Uranyl acetate and lead citrate, X 75000).

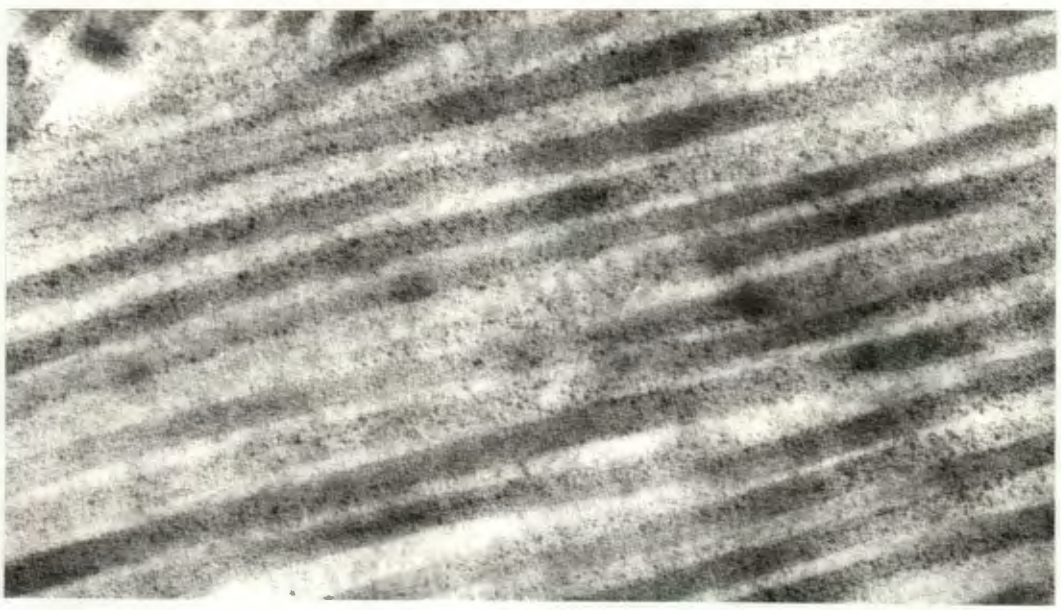

Figure 16.6 : Ultrastructural appearance of a cusp belonging to a Mitroflow valve ("pilot study", valve 1010) 71 days post-implantation. The collagen fibres appear less well preserved than in the control valve and many have lost their periodicity. (Uranyl acetate and lead citrate, X 75000).

SCANNING ELECTRON MICROSCOPY

Scanning electron microscopy was performed upon 3 Mitroflow valves which had been implanted for 6, 36 and 122 days. These valves came from the "original pilot" series, the "F process" group and the "pre-human" series respectively. The contact surface of all three valves showed minimal fibrin and platelet deposition in the areas examined. The surface of the cusps consisted of bare collagen fibre bundles without any mesothelial cell covering. The scanty cells present on the surface of the cusps (see Frontispiece) included erythrocytes, histiocytes and lymphocytes.

CALCIFICATION ANALYSIS

Quantitative analysis (method unknown) of the amount of calcium within xenograft cusps was performed by Mitral Medical Inc. and the results were made available to me (please see Table 16.5).

TABLE 16.5 : CALCIFICATION ANALYSIS OF MITROFLOW AND CONTROL VALVES (+/- S.D.)

	DURATION (DAYS)	µg/mg
PRE-HUMAN VALVES(N=5)	96 +/- 82.2	0.81 +/- 0.70
"F PROCESS" VALVES(N=7)	209 +/- 107.9	0.93 +/- 1.5
"G PROCESS" VALVES(N=12)	277 +/- 101.1	1.30 +/- 1.6
IONESCU-SHILEY VALVES(N=4)	106 +/- 65.6	2.50 +/- 0.7

COMBINED MITROFLOW BIOPROSTHESES

All 35 Mitroflow xenograft valves combined gave a mean percentage reduction of valve orifice area of 47.6% (S.D. =

20.8), which differed significantly from the 4 control valves (p less than 0.01). The Mitroflow valves had a mean pre-sacrificial trans-valvular gradient of 11.3 mm Hg (S.D. = 6.6) ; this did not differ significantly from the controls.

(v)IONESCU-SHILEY PERICARDIAL VALVES USED AS CONTROLS

The 4 Ionescu-Shiley valves were implanted in the 4 host baboons for a mean period of 128 days (S.D.= 71), with a range of 31-181 days. Three of the valves were placed in the mitral position and one in the tricuspid position. One valve had abundant fibrin thrombus on the convex surface of the cusps, especially at the contact zone and the remaining 3 valves showed only scanty thrombus with a similar distribution. An erosive host tissue overgrowth was noted in only one of the bioprostheses. Two of the valves showed attachment to the host's endomyocardium. Pre-sacrificial cardiac catheterization data in this group showed a mean percentage valve orifice reduction of 21.3% (S.D.= 12.6%) with a range of 8-33%.

COMMENT

The present study shows that the Mitroflow valves give poorer results in the baboon than those purported in the dog(1). The 4 Ionescu-Shiley xenograft valves (an admittedly small control group) gave better results than did the various groups of Mitroflow valves either singly or in combination (Table 16.3). It will be observed that the various categories of Mitroflow valves gave an improved performance with each new process of preparation that was introduced. The only exception to this trend is provided by the second group (prepared by" process G") and this is probably due to the fact that this group had a much longer pre-sacrificial survival period than

the other groups. This allowed more time for the progression of such valve-related complications as thrombosis, organization of thrombus and host tissue overgrowth. The latest ("pre-human") model of the Mitroflow valve tested showed no significant differences from the control valves with respect to percentage reduction in valve orifice area or in trans-valvular gradient immediately prior to sacrifice. However,it should be noted that the Ionescu-Shiley valves used were all size 19 mm diameter, whereas the Mitroflow valves were all size 21 mmm in diameter. The control valves were thus more stenotic ab initio.

With regard to percentage valve orifice area reduction, significant differences were found when the following groups of animals were compared (Table 16.3) : pilot study valves versus Ionescu-Shiley control valves ; "G" process valves versus "F" process, pre-human and control valves. Groups of baboons showing significant differences with regard to valve gradients were as follows : pilot study versus "F" process, pre-human and control groups ; "G process" versus "F process", "pre-human" and controls.

Fifteen out of the 35 Mitroflow valves (43%) had moderate or abundant non-infected thrombotic deposits on the prosthesis. This bulky thrombus appeared to play a role in the reduction of prosthetic valve orificial area and the development of increased trans-prosthetic gradients. The thrombus was virtually always confined to the inflow aspect of the xenograft cusps and was situated at and immediately proximal to the contact zones of the cusps. The thrombus usually involved all 3 cusps equally and presented a characteristic tri-radiate pattern ("Mercedes-Benz sign") when the prosthesis was viewed on the inflow aspect. Host tissue overgrowth appeared to be the second important mechanism leading to increased trans-valvular gradients.

Another factor which may influence the results of valve replacement is the experience of the operating surgeon. In the "pre-human" series of Mitroflow valves several of the valves

were implanted by a less experienced surgeon than was the case with the other valves. This resulted in a number of technical-related problems e.g., poor positioning of the prosthesis in the mitral valve ring (2 cases), and snaring of a suture over a stent post with deformation of the juxta-commissural portions of the 2 attached cusps.

The scanty calcification observed in 2 of the Mitroflow valves may serve to indicate that this prosthesis shares the tendency for cuspidal calcification of other glutaraldehyde-treated xenograft valves(3-5).

CHAPTER 17.

MISCELLANEOUS ASPECTS OF THE PATHOLOGY OF HEART VALVE REPLACEMENT

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MISCELLANEOUS ASPECTS OF THE PATHOLOGY OF HEART VALVE REPLACEMENT

A.PATHOLOGY OF THE ATRIO-VENTRICULAR SYSTEM OF HIS-TAWARA IN PROSTHETIC HEART VALVE REPLACEMENT

This study of the His-Tawara system was undertaken in an attempt to find a pathological cause for the unexplained sudden deaths which occur following heart valve replacement. In many such patients no cause is found,even at autopsy. Such deaths are commonly attributed to arrhythmia.

An haematoma in the inter-atrial septum is a not infrequent finding in hearts with recently inserted mitral valve prostheses. In some instances the haematoma (Fig. 17.1) may reach a diameter of several centimetres and even extend downwards to the vicinity of the atrio-ventricular node (A.V.N.) and bundle of His. The bundle(1) is also at risk during valve replacement, as it penetrates the central fibrous body,which unites the contiguous fibrous rings of the tricuspid, mitral and aortic valves(2,3). In the light of this, it was decided to examine the vulnerable proximal portion of the His-Tawara system of a series of 36 patients who died following heart valve replacement to see if any lesion could be found to explain their demise. Twenty-seven of these 36 patients have been previously reported(4). The methods used in this study are described in the Methodology section. A further series of 14 control hearts from routine autopsies was examined in an identical manner.

Figure 17.1 : Darkly-stained inter-atrial septal haematoma has extended downwards to reach the upper portion of the atrio-ventricular node. (Haematoxylin-eosin, X 60).

RESULTS

The main clinical and pathological findings in the 36 patients who came to autopsy following heart valve replacement,are summarized in Tables 17.1, 17.2 and 17.3. The patients who died after valve replacement and whose conduction system was studied, ranged in age from 9 to 66 years, with a mean age of 41 years (S.D.= 16.9). The patients in group A (Table 17.1) all died less than 14 days post-operatively. Conduction system haemorrhage was observed in 12 out of these 22 patients, mainly within the bundle of His. In 11 out of the

12 patients the blood tracked along the connective tissue within and around the conducting tissue in a manner similar to that described by Hudson(2). The earliest death in the group B patients (Table 17.2) occurred 14 days after valve replacement and the latest at 8 years. None of the group B patients showed evidence of recent conduction system haemorrhage. However, the haemosiderin deposits within the bundle branches of patients 23 and 24 probably indicates previous haemorrhage. Haemosiderin was also observed within the His bundle of patient 27, but this appeared to be related to trauma by a surgical suture, which passed through the A.V.N. In most of the patients in group B the cause of death was readily apparent at autopsy, apart from 3 patients (numbers 27,29 and 34) in whom the cause of death was unknown. In group A the cause of death was unknown in 11 out of the 22 patients. Haemorrhage into the conducting tissue was present in only 6 out of these 11 patients for whom no cause of death had been found at autopsy.

There was no sign of conduction tissue haemorrhage,past or present,in the 14 control hearts. The conducting tissue haemorrhage noted in group A patients, appeared separate in most instances from the larger and more obtrusive haemorrhage frequently observed in the inter-atrial septum following mitral valve replacement. In most hearts the conduction system haemorrhage was limited in extent,whereas in others it was more extensive and appeared to disrupt the conducting tissues. In some of these latter cases the haemorrhage was visible to the naked eye. Haemorrhages were noted within the His bundle in 9 out of the 22 group A patients and in the A.V.N. in 5 of the same 22 patients. Four patients had haemorrhages within the left bundle branch and 6 had right bundle branch haemorrhages. In only 2 of the group A patients did the ventricular myocardial histology show any signs of acute myocardial damage, which might have led to death due to dysrhythmia. Overall, twelve out of the 22 group A patients showed haemorrhage at some site within the His-Tawara system.

TABLE 17.1 : CLINICOPATHOLOGICAL DETAILS OF 22 EARLY (LESS THAN 14 DAYS) POST-OPERATIVE DEATHS (GROUP A)

PT.	AGE,RACE,SEX (YRS)	VALVES REPLACED	PROSTHESIS	SURVIVAL (DAYS)	HISTOLOGY OF HIS-TAWARA SYSTEM A.V.N.	HIS BUNDLE	L.B.B.	R.B.B.
1	9,B,M	M	S-E	0	H	H	N	H
2	29,W,F	A,M	S-E,UCT	0	C	H	H	N
3	50,C,M	A	C-E	0	N	H	N	N
4	82,W,F	A	C-E	0	N	N	N	N
5	43,W,M	M	UCT	0.125	N	N	N	N
6	46,B,M	M	UCT	0.17	N	N	N	N
7	15,W,F	A	UCT	0.3	N	N	N	N
8	16,C,M	A,M,T	UCTX3	0.4	H	H	H	H
9	58,W,F	A	UCT	0.8	C	H,S	H,S	N
10	42,W,F	M	UCT	1.0	N	N	N	N
11	14,C,M	A	LILL	1.0	N	N	C	N
12	31,W,M	M,T	UCT,S-E	1.0	N	H	N	H
13	61,W,F	A	LILL	1.0	N	N	N	H
14	60,W,M	A	UCT	1.5	N	N	N	H
15	41,W,M	A	LILL	1.5	N	N	N	N
16	28,C,F	M	UCT	2.0	-	N	N	-
17	44,W,M	M	S-E	2.0	H	H	H	N
18	66,W,M	A	UCT	3.0	N	H	-	H
19	47,C,F	M	S-E	4.0	H	H	H	-
20	22,W,M	A,M	B-S,S-E	5.0	H,S	N	N	N
21	52,W,F	M	UCT	5.3	-	N	N	N
22	62,W,M	A	SJM	12.0	H	N	N	N

AGE,RACE,SEX:B=BLACK,C-COLOURED,W=WHITE;M=MALE,F-FEMALE.
VALVES:A=AORTIC,M=MITRAL,T=TRICUSPID.PROSTHESES:UCT=UNIVERSITY OF CAPE TOWN,S-E=STARR-EDWARDS,C-E=CARPENTIER-EDWARDS,LILL=LILLEHEI-KASTER,B-S=BJORK-SHILEY,SJM=St JUDE MEDICAL.HISTOLOGY:C=CONGESTION,H=HAEMORRHAGE,N=NORMAL,-=NOT SEEN,S=SUTURE MATERIAL.AVN=ATRIOVENTRICULAR NODE,LBB=LEFT BUNDLE BRANCH, RBB=RIGHT BUNDLE BRANCH.

TABLE 17.2 : CLINICOPATHOLOGICAL DETAILS OF 14 LATE (GREATER THAN 14 DAYS) POST-OPERATIVE DEATHS (GROUP B)

PT.	AGE,RACE,SEX (YRS)	VALVES REPLACED	PROSTHESIS	SURVIVAL (DAYS)	HISTOLOGY OF HIS-TAWARA SYSTEM A.V.N.	HIS BUNDLE	L.B.B.	R.B.B.
23	49,W,M	A	UCT	15	-	ABSCESS	-	IRON
24	41,W,M	A	UCT	42	-	IRON	IRON	-
25	40,W,M	A	S-E	60	N	N	N	N
26	57,W,F	A,M	UCT,S-E	165	-	N	N	N
27	40,W,M	M,T	UCTX2	180	S,IRON	IRON	N	-
28	35,C,M	A	UCT	180	N	N	N	N
29	36,C,F	M	UCT	300	-	N	N	N
30	16,B,F	M	S-E	330	N	N	N	N
31	23,C,F	M	UCT	480	N	N	N	N
32	52,W,M	A,M	UCTX2	540	-	N	N	-
33	34,C,F	M	UCT	730	C	N	-	-
34	61,W,M	A	UCT	1095	-	N	N	N
35	27,C,F	A,M	UCT,S-E	1825	N	N	N	-
36	48,W,F	M,T	UCT,S-E	2920	N	N	N	N

SAME ABBREVIATIONS AS USED IN TABLE 17.1.

TABLE 17.3 : PRINCIPAL CAUSES OF DEATH IN 36 PATIENTS WHOSE HIS-TAWARA SYSTEM WAS EXAMINED HISTOLOGICALLY

GROUP A	
CAUSE UNKNOWN	11
ELECTROLYTE ABNORMALITY	1
UNRELIEVED PULMONARY STENOSIS	1
HEART BLOCK	1
THROMBOSED PROSTHESIS	1
STONE HEART	1
MYOCARDIAL FAILURE	2
CEREBRAL EMBOLISM	2
CORONARY OSTIAL OBSTRUCTION BY PROSTHESIS	2
GROUP B	
INFECTIVE ENDOCARDITIS	4
THROMBOEMBOLISM	3
CAUSE UNKNOWN	3
CATHETERIZATION ACCIDENT	1
CORONARY THROMBOSIS	1
DETACHED PROSTHESIS	1
THROMBOSED PROSTHESIS	1

COMMENT

It is significant that recent haemorrhage within the conduction system was only found in patients who died less than 2 weeks after heart valve replacement (Tables 17.1 and 17.2). Such haemorrhage is likely to be related to the operation. Although one is dealing with a small number of patients, there appears to be no significant difference in the incidence of conduction tissue haemorrhage when one compares the mitral and aortic prostheses.

The central fibrous body and membranous septum constitute a continuous structure and are formed by the contiguous tricuspid, mitral and aortic valve rings(2). The bundle of His penetrates the central fibrous body, and is thus at risk in operations on these valves. The bundle is said to be at greatest risk during aortic valve replacement(2). Haemorrhage into the conducting tissues may come about either as a result of direct surgical trauma, or as a result of anoxia. In patient 27, a suture passed through the centre of the conduction tissue in the region where the A.V.N. becomes the bundle of His. One can only speculate as to whether the haemosiderin and suture material within the conducting tissue may have caused electrical instability, leading to fatal arrhythmia. In patient 9, a suture was observed to divide the left bundle branch and to run close to the bundle of His, which showed haemorrhage.

Anoxia seems the likeliest cause of the conduction system haemorrhages noted in the other 11 patients in group A. Thung et al.(6) state that the conduction tissue is the most heavily vascularized portion of the heart, and hypoxia produces capillary wall changes, thereby increasing capillary permeability. Thus, hypoxia may be expected to produce selective haemorrhage into this area. An analysis of the clinical course of their patients, indicated that in each patient with haemorrhage not related to direct injury, a

significant period of hypoxia was a common denominator. They furnished experimental data to implicate hypoxia as a cause of haemorrhage into the cardiac conduction system, and emphasized the importance of adequate oxygenation in the post-thoracotomy patient. They also postulated that deposits of haemosiderin may remain within the conduction system, elicit scarring and produce arrhythmia.

My three patients (numbers 23,24 and 27) of group B who had haemosiderin deposits (without fibrosis) within their conduction tissues had survived 2 weeks, 6 weeks and 6 months respectively. Patients 23 and 24 died of infective endocarditis. Patient 27 showed no cause of death at autopsy and the only significant finding was a suture passing through the A.V.N.

Niles and Sandilands(7), found haemorrhage in the atrio-ventricular conduction system in 18 out of 26 early deaths after valve replacement with a Starr-Edwards prosthesis. Such haemorrhage was also present in 6 out of their 36 late deaths. Most of their 24 cases of conduction tissue haemorrhage had shown an inadequate post-operative cardiac output, and they regarded the haemorrhages as a possible cause of fatal post-operative heart failure. My findings confirm their impression that haemorrhage commonly occurs in the atrio-ventricular conduction tissue after valve replacement.

It is possible that a more detailed (serial section) examination of the conduction system in my 50 patients might have revealed other pathological changes, including further instances of haemorrhage. A preliminary investigation of the His-Tawara system in several patients who died after cardiac surgery for lesions not necessitating valve replacement (e.g., saphenous vein grafting of coronary arteries), but involving similar periods of time on cardio-pulmonary bypass, also showed instances of haemorrhage into the His-Tawara system. This may indicate that the relative hypoxia of the bypass procedure is of greater significance than direct surgical

trauma in the aetiology of such haemorrhage. A recent monograph for cardiac surgeons describes the anatomy of the conduction system in a variety of cardiac abnormalities(8).

It is apparent that haemorrhage into the conduction tissue is a not uncommon finding in patients dying 12 days or less after heart valve replacement, and hypoxia is the likely cause. Such haemorrhage cannot be blamed for causing sudden, unxpected death in the early post-operative period, since it was only present in about half of such sudden death patients. According to Froysaker et al.(9) the clinical manifestation of haemorrhage in the atrio-ventricular conduction system is left bundle branch block followed by A-V block and ventricular arrhythmia in the early post-operative period.

B. RENAL HAEMOSIDEROSIS IN PATIENTS WITH PROSTHETIC HEART VALVES

Haemolytic anaemia associated with an intra-cardiac prosthetic valve was reported for the first time by Rose et al.(1) in 1954. This complication was confirmed experimentally in dogs by Stohlman et al.(2) in 1956. While many subsequent reports dealing with the clinical and haematological aspects of haemolysis associated with intra-cardiac valve prostheses have been published(3-22), few refer to concomitant renal haemosiderosis(23-25). Renal siderosis is the anatomical indicator of intra-vascular haemolysis(23). When an excessive amount of iron is liberated into the blood by intra-vascular haemolysis, it is deposited exclusively in the kidneys and none is evident in the liver or spleen. In the rare instance where the anaemia becomes severe and requires repeated blood transfusions, haemosiderosis may be observed in many organs(26). Needle biopsy of the kidney has been used to diagnose renal siderosis in the haemolytic anaemias(27).

Haemolytic anaemia on a mechanical basis has been a problem, particularly in patients with cloth-covered non-tissue, cardiac valve prostheses(26). Haemolysis is believed to result from two major factors : the "hammer-and-anvil" effect resulting from damage to the erythrocytes by closing of the occluder upon the metallic ring ; and the abrasion or friction effect of a jet stream of blood against an irregular fabric surface, especially in cloth-covered valves. The first of these can be eliminated by having the occluder rest on small metallic struts rather than on a circular metal ring. The second may be reduced by having all parts of the valve except the sewing ring made of smooth highly polished material. Studies on patients with native valvular heart disease(6,28-31), especially aortic stenosis(30) and incompetence(32), has revealed the presence of intra-vascular haemolysis. Mechanical haemolytic anaemia has also been reported after repair of ruptured chordae

tendineae of the mitral valve apparatus(33). Haemolysis resulted from the whiplash motion of the loose ends of the ruptured chordae and the disrupted suture material attached to the mitral valve apparatus. Since the incidence of renal haemosiderosis in our patients with valve prostheses was unknown, I decided to examine the incidence and severity of renal siderosis in autopsied patients with heart valve prostheses, as well as in a group of patients with severe rheumatic-type valvular deformities and a routine autopsy control group. The iron content of 'normal' kidneys appears to be a neglected topic, and a standard reference on the histology and chemistry of tissue iron(34) gives no information regarding the iron content of 'normal' kidneys.Deatils of the methods used in this study of prosthesis-related renal haemosiderosis are given in the Methodology section.

RESULTS

PATIENTS WITH IMPLANTED HEART VALVE PROSTHESES

The incidence and severity of renal haemosiderosis in the autopsied 105 patients with implanted prosthetic valves is given in Tables 17.4 and 17.5. Large (+++) amounts of iron (Figs. 17.2 and 17.3) were present in the kidneys of 9 out of the 105 patients,(8.6%). The haemosiderin granules were usually seen within the cells of the proximal convoluted tubules (Fig. 17.3), but in in some instances the iron was also present in the epithelial cells of the glomeruli. This distribution is similar to that observed by Roberts and Morrow(23). Rarely, iron was seen lying free within Bowman's space or in the interstitium. No significant amount of iron was seen in the liver or spleen of any of these 105 patients.

Table 17.6 gives details of the 9 patients with abundant renal siderosis. The 2 patients with a U.C.T. aortic prosthesis both survived one month after operation. One died

of cardiac failure and the other had an unidentified fungal

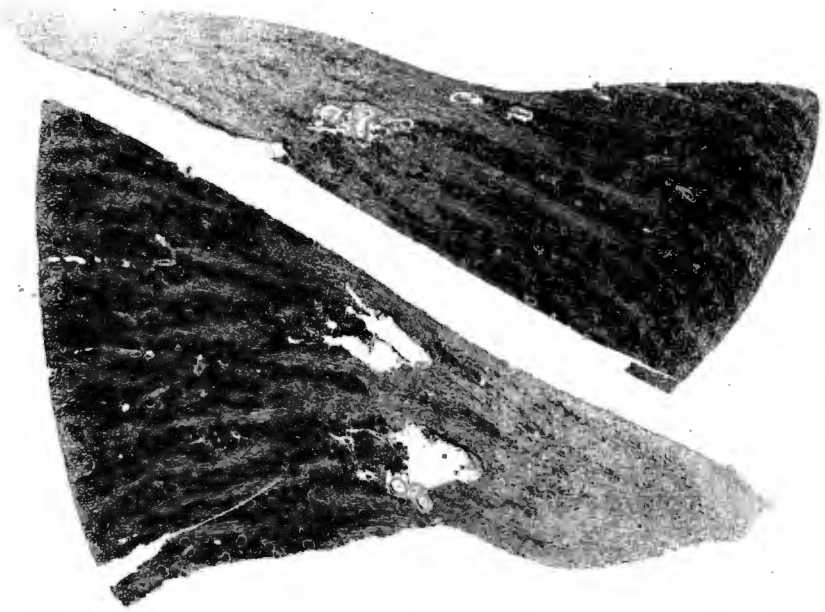

Figure 17.2 : Abundant (+++) renal cortical siderosis in patient 1 with multiple UCT prostheses. (Perl's potassium ferrocyanide reaction, X 5).

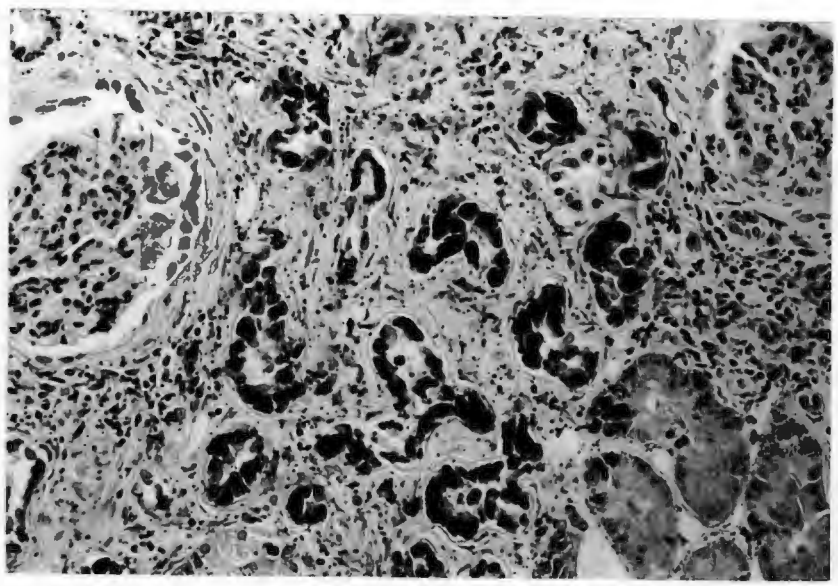

Figure 17.3 : Prominent iron deposits are seen within the epithelial cells of the proximal convoluted tubules. (Perl's potassium ferrocyanide reaction, X 150).

infection of the prosthesis. A third patient had infected vegetations on her U.C.T. aortic and mitral prostheses and bacteriological culture grew Candida parasilosis. Death was due to a cerebral embolus. One patient with a U.C.T. mitral prosthesis had a 0.2 cm. wide endothelial-lined para-valvular defect, which would have caused mild incompetence. Death was again due to a cerebral thromboembolus. No thrombi were found on the prosthesis or anywhere else within the heart. A fifth patient with normal U.C.T. aortic, mitral and tricuspid prostheses, died of bilateral lobar pneumonia. Her prothrombin index had been very low (less than 10%) and intra-pulmonary haemorrhage was also present. Both patients with Starr-Edwards mitral prostheses had severe wear of the cloth covering the base ring of their prostheses. Extensive areas of both base rings showed bare metal where the cloth had been worn away. Abundant thrombus covered the bare metal, which was only revealed once the thrombus had been removed. Both patients died of thromboembolism. Patient 4 (Table 17.6) with abundant renal siderosis had a U.C.T aortic and a Starr-Edwards mitral valve prosthesis inserted at the same time. Death occurred 150 days post-operatively due to a fulminating rheumatic myocarditis and pneumonitis.

Haematological data were obtainable retrospectively in 5 out of the 9 patients with prominent renal siderosis (patients numbers 2,3,5,6,and 7). If the normal haematocrit for males is 39-45% and that for females 35-40%, then 3 out of these 5 patients (Nos.3,6,and 7 in Table 17.6) were anaemic shortly before death. Two of these anaemic patients had normal pre-operative haematocrits, while no haematocrit was available in the third patient (No. 7). Patients 3 and 7 had fragmented red blood cells in their peripheral smears 2 months post-operatively.

Moderate amounts of renal iron (++) were demonstrated in 17 out of the 105 patients with prostheses. One of these patients was a 28-year-old female with a Starr-Edwards mitral

prosthesis who died only 2 days after operation. It is possible that her renal siderosis antedated the valve replacement operation. The other 16 patients had their prostheses implanted from 27 to 1440 days. Scanty amounts of iron (+) were noted in the kidney sections of 26 patients and 53 showed no evidence of renal siderosis (Table 17.4).

TABLE 17.4 : INCIDENCE AND SEVERITY OF RENAL SIDEROSIS IN 105 AUTOPSY PATIENTS WITH HEART VALVE PROSTHESES

PROSTHESES	RENAL IRON CONTENT			
	NIL	SCANTY (+)	MODERATE (++)	ABUNDANT (+++)
UCT-A	14	7	2	2
UCT-M	5	9	5	1
UCT-MULTIPLE	3	1	0	1
TOTALS	22	17	7	4
MIXED	8	2	4	3
S-E-M	4	3	4	2
S-E-A	0	1	0	0
TOTALS	4	4	4	2
LILL-M	3	0	0	0
LILL-A	4	0	0	0
TOTALS	7	0	0	0
B-S-A	2	1	0	0
HANC-M	3	0	0	0
C-E-A	1	1	0	0
C-E-M	2	1	0	0
TOTALS	3	2	0	0
SJM-A	2	0	0	0
SJM-M	1	0	1	0
SJM-A+M	1	0	1	0
TOTALS	4	0	2	0
No. PATIENTS	53	26	17	9

GRAND TOTAL = 105

UCT=UNIVERSITY OF CAPE TOWN,S-E = STARR-EDWARDS,LILL=LILLEHEI, B-S=BJORK-SHILEY,HANC=HANCOCK,C-E=CARPENTIER-EDWARDS,SJM=St JUDE
MEDICAL,A=AORTIC,M=MITRAL.

TABLE 17.5 : INCIDENCE AND SEVERITY OF RENAL SIDEROSIS IN 105 AUTOPSY PATIENTS WITH PROSTHETIC HEART VALVES

	RENAL IRON CONTENT			
PROSTHESIS	NIL	SCANTY (+)	MODERATE (++)	ABUNDANT (+++)
UCT (N=50)	22	17	7	4
MIXED(N=17)	8	2	4	3
S-E (N=14)	4	4	4	2
LILL (N=7)	7	0	0	0
B-S (N=3)	2	1	0	0
HANC (N=3)	3	0	0	0
C-E (N=5)	3	2	0	0
SJM (N=6)	4	0	2	0
TOTALS	53	26	17	9

GRAND TOTAL =105

TABLE 17.6 : DATA ON PATIENTS WITH VALVE PROSTHESES AND ABUNDANT RENAL HAEMOSIDEROSIS

PT.	AGE(yr), SEX	PROSTHESIS TYPE	POST-OP. SURVIVAL(DAYS)	PROSTHESES AT AUTOPSY	CAUSE OF DEATH
1.	41,M	UCT-MULTIPLE	27	+THROMBUS	C.A.DISSN
2.	20,F	UCT-A	30	NORMAL	CCF
3.	48,M	UCT-A	30	INFECTED	BRAIN INF
4.	14,M	MIXED	150	+THROMBUS	ACUTE RH F
5.	39,F	UCT-A+M	180	INFECTED	BRAIN INF
6.	22,F	UCT-M	330	P-V LEAK	BRAIN INF
7.	43,F	UCT-MULTIPLE	720	NORMAL	PNEUMONIA
8.	24,F	S-E-M	795	CLOTH WEAR	C.A.EMBOLUS
9.	25,F	S-E-M	2880	CLOTH WEAR	BRAIN INF

M=MALE,F=FEMALE,UCT=UNIVERSITY OF CAPE TOWN,A=AORTIC,M=MITRAL, S-E-M=STARR-EDWARDS,P-V=PARA-VALVULAR,C.A.=CORONARY ARTERY, CCF=CARDIAC FAILURE,INF=INFARCT,RH F=RHEUMATIC FEVER.

TABLE 17.7 : AUTOPSY INCIDENCE OF RENAL SIDEROSIS IN 53 CONTROL PATIENTS

VALVE LESION	RENAL IRON CONTENT	
	NIL	SCANTY
MITRAL STENOSIS/INCOMPETENCE	25	1
AORTIC STENOSIS/INCOMPETENCE	6	0
ROUTINE AUTOPSIES (NORMAL VALVES)	21	0

CONTROL PATIENTS

Renal haemosiderosis was absent in 31 of the 32 control patients who died with advanced rheumatic-type valvular deformities (Table 17.7). The only control patient showing renal siderosis was a 57-year-old white male who had mitral stenosis, trivial aortic stenosis and functional tricuspid incompetence. Cardiac symptoms had been present for 10 years. This same patient had large amounts of iron in his liver and spleen too, and as no blood transfusions had been given, this suggested that he had a generalized haemosiderosis and that the renal siderosis was not due to intra-vascular haemolysis. None of the 21 routine adult autopsy cases (Table 17.6) showed renal siderosis.

COMMENT

Significant (i.e. of moderate or severe degree) renal haemosiderosis was present in 26 of the 105 autopsy patients (25%) with valvular prostheses. The nine patients with +++ renal siderosis included 2 patients with severe sewing ring cloth wear and one patient with a small para-valvular leak. Three patients had thrombi on the prosthesis (infected in two). The remaining 2 patients showed no abnormality related to the prosthesis. Ten out of the 17 patients with ++ renal siderosis showed no abnormality of their prosthetic valves. Five others had abundant thrombi on the prostheses (infected in one case). One patient had a small para-valvular leak alongside a St Jude Medical mitral valve prosthesis. The

remaining patient had normal St Jude Medical mitral and aortic valve prostheses. During surgery the knife had made a small communication between the left ventricle and the right atrium (acquired Gerbode defect). This had been closed during the operation by a single suture with a pledget placed on the right atrial side. It is doubtful whether the latter event played any role in the patient's subsequent development of renal siderosis.

Thus, in 12 patients, significant renal haemosiderosis was observed in the absence of any abnormality of the prosthesis. All 7 of Roberts and Morrow's(23) cases with renal siderosis had malfunctioning flexible Teflon aortic valves and haemolytic anaemia. Niles and Sandilands(24) encountered renal siderosis in 4 out of 26 early deaths and in 17 of 36 late deaths following heart valve replacement with Starr-Edwards prostheses. The latter authors did not indicate the degree of the renal haemosiderosis nor did they specify the state of the prosthetic valves in such patients.Both groups of authors agree that renal haemosiderosis does not impair renal function. Crexells et al.(35), however, point out that the long-term effects of haemosiderinuria have not yet been adequately documented. Others also comment on haemolysis in patients with Starr-Edwards prostheses(36,37). Previous studies(6,7,38) have revealed haemolysis in patients whose prosthetic valves have shown no clinical evidence of incompetence.Postmortem renal siderosis may show clinically unapparent intra-vascular haemolysis.

Davies(39) states that slight amounts of haemolysis are common with all mechanical valves. Mechanical valves appear to produce more severe haemolysis than xenograft valves with a similar degree of clinical incompetence(40). Significant haemosiderosis (i.e. ++ or +++) was only observed in mechanical valves in my study and none of the cases with xenograft valves examined showed such a degree of siderosis. Several authors discuss haemolysis associated with xenograft replacement of cardiac valves(40-47). Rao et al.(44) conclude

that porcine xenograft valves do not seem to be associated with haemolysis unless complicated by a para-valvular leak. Intra-vascular haemolysis may be associated with porcine mitral valve calcification in children(47).

The present autopsy study showed renal haemosiderosis in 56% of patients with University of Cape Town prostheses, (in 44% with aortic prostheses and in 75% of those with mitral prostheses), 53% of patients with multiple mixed prostheses, 71% of patients with Starr-Edwards prostheses, 33% of patients with Bjork-Shiley prostheses, 67% of patients with St Jude Medical prostheses,and 40% of patients with Carpentier-Edwards prostheses. None of the small number of patients examined with Lillehei-Kaster or Hancock prostheses showed renal siderosis.Crexells et al.(35) detected subclinical haemolysis in 67% of their 208 patients with valvular prostheses. Rao et al.(45) reported that in isolated mitral valve replacement 66% of Lillehei-Kaster valves showed associated compensated haemolysis compared with 42% in Bjork-Shiley valves, 85% in Starr-Edwards valves and none in frame-mounted homografts.

Only one of the 290 patients with prostheses studied in this work had gallstones. The patient was a 67-year-old female with a St. Jude Medical aortic valve prosthesis. Surprisingly, her kidneys showed no evidence of siderosis. Harrison et al.(48) have shown that the prevalence of gallstones in patients with heart valve prostheses is significantly greater than in patients with mild or severe valvular heart disease without valve replacement. Apparently the formation of gallstones may result from even mild mechanical haemolysis. These authors suggest that valve prosthesis recipients should be evaluated carefully for symptoms of gall-bladder disease at periodic intervals, especially late after valve replacement. They also recommend that gallstones removed from prosthetic heart valve patients at surgery or at autopsy be analysed for chemical composition, especially to determine the existence of higher than average bilirubin content. The present autopsy study does not support Harrison et al.'s contention that

cholethiasis is a frequent complication of artificial heart valve replacement.

Initially it was believed that the haemolysis in patients with prosthetic heart valves always has a 'mechanical' or traumatic basis(2). There is evidence that the erythrocyte damage may not result simply from the mechanical trauma of poppet action on the red cells, but that haemodynamic disturbances, such as turbulent blood flow and shearing stress resulting from rapidly changing velocity and pressure, are the most important causes of traumatic mechanical damage(6,49,50). These factors and the interaction of red blood cells with the valve materials and with fibrin deposits around the valve, are probably all involved to some degree(51).

The degree of urinary iron loss from continued intra-vascular haemolysis may be severe and may even lead to chronic iron deficiency and superimposed iron deficiency anaemia(36,52). Much less common after valve replacement is haemolysis of the auto-immune type, with a positive anti-globulin test. The cause of this haemolysis is unknown(53,54).

C.SUBVALVULAR LEFT VENTRICULAR FALSE ANEURYSM COMPLICATING MITRAL VALVE REPLACEMENT.

Aneurysms of the left ventricle usually are a consequence of myocardial infarction(1,2) and the great majority are true aneurysms with myocardial remnants in their wall. Other causes of left ventricular aneurysm include trauma and rarities such as syphilis, tuberculosis, and mycotic aneurysms. False aneurysms may occur after non-fatal rupture of myocardial infarction. Idiopathic aneurysms in the submitral, subaortic or apical regions of the left ventricle have been reported, predominantly from Africa(3-5). It has been suggested that the idiopathic aneurysms may develop because of defects in the attachment of the left ventricular myocardium or aorta to the fibrous mitral and aortic annuli.

Valve replacement surgery may cause a similar loss of atrio-ventricular continuity. Rupture of the heart at the atrio-ventricular sulcus is a rare complication of excessive excision of the mitral annulus during mitral valve replacement(6-10). Extension of valvular calcification into the annulus will predispose to this complication. Such disruption will lead to the formation of a sub-epicardial haematoma over the defect. Enlargement of the haematoma may compress the coronary sinus. In the absence of pericardial adhesions, rupture through the epicardium is likely. If the sub-epicardial haematoma undergoes organization instead of rupture, one may have the formation of a false cardiac aneurysm communicating with the left ventricle through the defect in the mitral annulus. Surgical repair of such an aneurysm diagnosed during life has been reported(11-16). Amongst the 272 autopsied patients with heart valve prostheses studied in this work, two patients were encountered who illustrate how excessive mitral ring excision may lead to the formation of a sub-epicardial haematoma and a sub-valvular false aneurysm. These two patients have been previously reported(10). A variety of surgical approaches have been used for the repair of this grave complication(17).

CASE REPORTS

CASE 1.

A 54-year-old woman had severe rheumatic mitral stenosis with mild mitral incompetence. The mitral valve showed some calcification and the orificial area was 0.4 sq. cm. Operation revealed thrombus lining the wall of a small left atrium. The stenotic mitral valve was split, but was not found to be salvageable. The valve was excised and replaced by a No. 19 glutaraldehyde-preserved (Hancock) xenograft. Most of the thrombus was removed from the atrium. The patient did well for three hours post-operatively, but then arrhythmia developed followed by circulatory collapse resulting from massive intra-thoracic haemorrhage and the patient died.

Autopsy revealed a 1.5 cm. wide defect at the left of the mitral annulus immediately inferior to the sewing ring of the prosthesis. A 2.5 cm. diameter sub-epicardial haematoma occupied the left atrio-ventricular groove immediately over the defect (Fig. 17.4). At the summit of the haematoma there was a small hole in the epicardium through which the fatal haemorrhage had occurred. Histology revealed fibrin deposition on the bare myofibres at the rupture site and an overlying sub-epicardial haematoma. Haemorrhage extended into the adjacent myocardium. There was no evidence of organization of the haematoma as death had occurred only 3 hours post-operatively.

CASE 2.

A 58-year-old woman had severe mitral stenosis and incompetence (mitral valve area 0.49 sq. cm.). The valve was calcified and so, too, was the wall of the left atrium. The chamber contained much thrombus. The mitral valve was excised

with difficulty because of extensive calcification of the posterior cusp. A 4M Starr-Edwards prosthesis was inserted. A tricuspid annuloplasty was also performed. Fresh thrombus and calcium were removed from the wall of the left atrium. Her post-operative course was uneventful. Death occurred four years post-operatively because of cerebral thromboembolism.

At autopsy, bland thrombi were present on the sewing ring and struts of the Starr-Edwards prosthesis. Immediately below the posterolateral portion of the sewing ring was an 8-mm. diameter rounded ostium that communicated with a fibrous-walled aneurysm (Fig. 17.5). The latter occupied the left posterolateral atrio-ventricular groove and was filled with blood. The aneurysm measured 4 X 3 X 2 cms and lay within the epicardium. It had displaced the left circumflex coronary artery slightly downward without compressing the vessel. The coronary arteries were free of intrinsic disease. The aneurysm wall consisted of acellular collagen with foci of calcification. A thin layer of fibrin thrombus was present on its inner aspect.

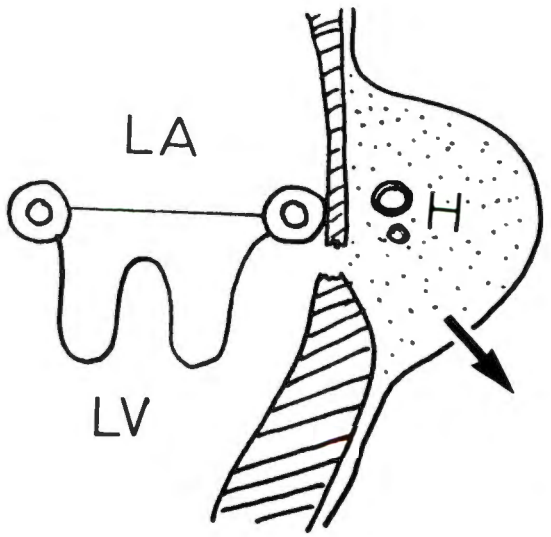

Figure 17.4 : Diagram of sub-epicardial haematoma in patient 1, which resulted from excessive resection of mitral valve ring tissue. Rupture of overlying epicardium led to fatal haemorrhage.

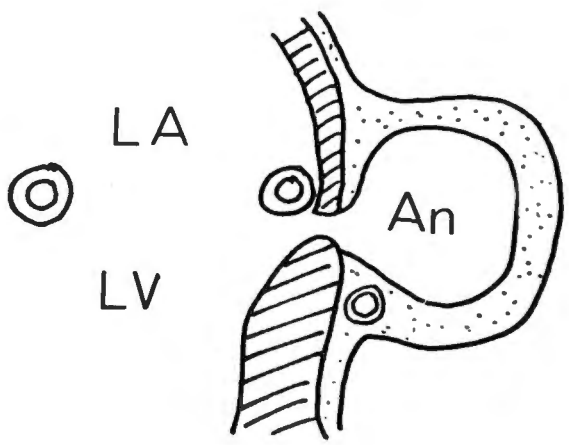

Figure 17.5 : Intra-epicardial false aneurysm of patient 2 communicates with left ventricle below the mitral valve prosthesis.

COMMENT

The left atrial myocardium is normally totally separated from the left ventricular wall. It is the mitral ring together with the endocardium and pericardium that maintain the anatomical continuity between the left atrium and the left ventricle. It has been suggested(6,11,12) that rupture of the left atrio-ventricular sulcus during valve replacement is more likely to occur if mitral leaflet calcification involves the mitral ring too. Attempts at excision of all of the calcium may produce rupture. Fibrous distortion of the posterior mitral leaflet, coupled with organized left atrial thrombus, may obliterate the exact limits of the annulus. Delayed rupture of the mitral annulus may also be produced by localized tissue necrosis resulting from prosthetic sewing ring sutures being placed too deeply into friable myocardium. In excising the mitral valve in a patient with a small left atrium, the exposure may be poor and a portion of the annulus may be inadvertently excised. After the valve is replaced and cardio-pulmonary bypass is terminated, the stage is set for disruption of the atrio-ventricular sulcus.

Excessive removal of a laminated thrombus on the left atrial wall may also lead to perforation if excessive clearance is done, since the wall landmarks are often obscured. Selection of an oversize valve, resulting in a tight fit in the annular ring, may stretch or tear the annulus(13,18). Re-excision of the annulus when removing a previously implanted mitral prosthesis can easily lead to perforation. Wolpowitz et al.(13) recommend that in such cases the prosthesis should be excised between the sewing ring cushion and its metal frame. Firmly embedded prosthetic cloth is left behind for use of placement sutures as if it were the annulus. The use of a curved metal instrument to define posterior chordal attachments may also cause a perforation of the ventricle next to the atrio-ventricular junction. The post-surgical false aneurysm has the potential for expansion

with pressure effects and perhaps rupture (either externally or into a cardiac chamber).

There are striking morphological similarities between post-surgical, subannular ventricular aneurysm and congenital submitral aneurysm. It is likely that both these types of aneurysm share a common pathogenesis, namely loss of attachment of the left ventricular myocardium to the fibrous mitral annulus. The cause of the loss of attachment in the so-called congenital aneurysm is unknown. Surgical trauma to the mitral valve ring is becoming more widely recognized as a possible cause of a intra-operative left ventricular wall rupture and a cardiac pseudo-aneurysm. Sub-valvular false aneurysm has also been described after aortic valve replacement (14,19).

The type of left ventricular wall rupture associated with mitral valve replacement described above has been referred to as type I rupture. The second type of rupture (type II) occurs in the posterior mid-portion of the left ventricle(13,20-28). Explanations for this problem(27) have included : (i) cutting too deep a plug and "button-holing" the ventricle during excision of the papillary muscle in a fragile, atrophic 'mitral ventricle'(12,18,29,30). (ii) Dissection of blood into the papillary muscle wound(29), (iii) trauma from apical venting(31), (iv) epicardial adhesions, (v) impingement of a prosthetic valve strut(21,23,25,26,29,31), (vi) intrinsic myocardial disease(18), and (vii) interruption of continuity between papillary muscle and mitral annulus. Cobbs et al.(27) suggest that a combination of factors may be important in the pathogenesis of this lesion. These factors included older patient age with associated coronary arterial disease, the size of the xenograft prosthetic valve, and the forceful central flow pattern of the Hancock valve. Cold- and potassium-induced cardioplegia render the heart more deformable and more liable to stretch-induced damage. The latter is favoured by excision of the mitral valve apparatus and too rapid weaning of the cardioplegic heart from bypass.

Cobbs et al(27) claim to have eliminated fatalities due to this complication by changing their operative technique to include a 30-minute period of empty beating after reversal of the cardioplegia.

False aneurysms may also be encountered at other sites after open-heart surgery. Jutrin et al.(32) described a false aneurysm of the right atrium, which appeared after open-heart surgery and appeared to be due to loosening of a right atrial suture. Because of the low pressure in the right atrium, the danger of rupture seemed to be low, and conservative therapy was chosen. Becker et al.(33) reported a patient who presented 12 months post-aortic valve replacement with a false aneurysm near the aortic cannulation site. The patient refused surgery and died shortly afterwards. Autopsy revealed a smooth-walled 1 cm. diameter defect adjacent to the cannulation site (presumably related to injury from a partial occlusion clamp).

Weesner et al.(34) described left ventricular aneurysms associated with intra-operative venting of the cardiac apex in 32% of 50 children (average age 8 years) who were consecutively catheterized after surgical repair of congenital heart disease. The left ventricular apex had been vented by a sump during cardiopulmonary bypass in each patient. The aneurysms varied in size, but were generally small. Avereage dimensions were 7.5 X 6.8 mm. in the anterior-posterior projection. The wall of the left ventricular apex was thinner in patients with aneurysms than in age- and lesion-matched controls. All of the left ventricular aneurysm patients were asymptomatic during average follow-up of 4 years. The authors conclude that such aneurysms may be a potential source of complications and, when possible, alternate methods for venting the left ventricle are recommended.

ADDENDUM :

At the time of writing (April 1984) I have just encountered a third autopsy patient with this complication. The patient was a 56-year-old female who underwent mitral valve replacement 7 years ago for calcific mitral stenosis due to repeated attacks of acute rheumatic fever. At the time of surgery the surgeon resected an excessive amount of the mitral valve ring and surrounding tissue and the circumflex branch of the left coronary artery was inadvertently damaged. The surgeon performed a saphenous vein coronary arterial bypass graft to the distal portion of the damaged vessel. The patient complied poorly with anticoagulant therapy and died of a cerebral haemorrhage with a pre-terminal prothrombin index of less than 10%. Autopsy revealed an inter-communicating, three chambered submitral false aneurysm in relation to the Starr-Edwards mitral prosthesis. The prosthesis had no annular tissue abutting against it at the site of the aneurysm.

D.INFECTIVE ENDOCARDITIS IN PATIENTS WITH PROSTHETIC HEART VALVES

Infective endocarditis was encountered in 31 out of the 275 patients with implanted cardiac valvular prostheses in this study and it accounted for 4.9% of the early deaths and 18.2% of the late deaths. There were 16 females, 15 males, 17 whites, 12 coloureds (mixed race), and 2 black patients. The mean age was 41.9 years (S.D.= 13.6) with a range of 15 to 67 years. The mean post-operative survival was 332 days (S.D. = 657) with a range of from 14 to 3285 days. The distribution was as follows : group 1 (early survivors) 7 (23%) and group 2 (late survivors) 24 (77%). Thirty of the cases were patients with mechanical prostheses and only one involved a tissue valve. (The solitary patient with a fascia lata prosthesis excluded from this analysed core group also had an infected prosthesis). The types of prosthetic valves affected are listed in Table 17.8. The diagnosis of prosthetic valve infection had not been suspected in 4 patients (13%).

TABLE 17.8 : TYPES & NOS.(%) OF INFECTED PROSTHETIC CARDIAC VALVES ENCOUNTERED AMONGST 275 PATIENTS WITH VALVE PROSTHESES.

UNIVERSITY OF CAPE TOWN	16 (13.3%)
LILLEHEI-KASTER	2 (12.5%)
BJORK-SHILEY	1 (6.7%)
STARR-EDWARDS	4 (8.5%)
St. JUDE MEDICAL	4 (13.8%)
MIXED TYPES OF VALVES	3 (5.8%)
CARPENTIER-EDWARDS	1 (2.6%)

Table 17.9 indicates the types of causative micro-organisms identified in these 31 patients with infected prosthetic heart valves. The commonest pathogens were Staphylococci, followed by gram negative bacilli and fungi. In

all of the patients with mechanical valves the infection was situated at the site of attachment of the prosthetic sewing ring to the native valve ring. The one infected (Carpentier-Edwards) tissue valve had infected vegetations on the cusps with minimal juxta-sewing ring inflammatory changes. Nearly all of the infected mechanical valves also had infected vegetations on the struts or cage. Ring abscesses were noted in almost one-third of cases (29%) and one of the 9 such patients developed complete heart block due to inflammatory destruction of the bundle of His.

TABLE 17.9 : CAUSATIVE MICRO-ORGANISMS IN 31 PATIENTS WITH PROSTHETIC VALVE INFECTIVE ENDOCARDITIS

ORGANISM	GROUP 1	GROUP 2	TOTAL
STAPHYLOCOCCUS ALBUS	0	7(23%)	7(23%)
STAPHYLOCOCCUS AUREUS	0	4(13%)	4(13%)
CANDIDA ALBICANS	2(7%)	1(3%)	3(10%)
CANDIDA PARASILOSIS	0	1(3%)	1(3%)
UNIDENTIFIED FUNGUS	1(3%)	0	1(3%)
KLEBSIELLA SPECIES	1(3%)	0	1(3%)
DIPHTHEROIDS	1(3%)	1(3%)	2(7%)
COLIFORMS	0	1(3%)	1(3%)
ACTINOBACILLUS	0	1(3%)	1(3%)
PSEUDOMONAS SPECIES	0	1(3%)	1(3%)
BACILLUS CEREUS	0	1(3%)	1(3%)
UNKNOWN	2(7%)	6(19%)	8(26%)

Three out of the 31 patients with prosthetic valve infective endocarditis had a clinical history of pre-operative infective endocarditis. Upon examining the surgical records of the University of Cape Town Pathology Department of Pathology, I was able to find reports and slides of only 6 out of the 31 patients who had their natural valves surgically excised. None

of theses 6 cases showed evidence of infection microscopically.

Seven of the patients with infected prostheses died due to malfunction of the prosthesis (5 had partially detached prosthetic valves, and 2 mitral prostheses were severely obstructed by vegetations). Ten patients died of systemic embolism ; 4 died of ruptured mycotic aneurysms, and 10 died of other causes e.g., myocardial failure or pyaemic abscesses and toxaemia.

COMMENT

Not all bacteraemias in patients with prosthetic heart valves represent infection of the valve(1,2), particularly when there is no haemodynamic instability or evidence of valve dysfunction and when the bacteraemia is due to a gram negative bacillus. Parker et al.(3) noted bacteraemia in 3.6% of 890 patients after heart valve replacement in the hospital recovery period. Only 2 out of the 32 bacteraemic patients developed endocarditis.

Leitersdorf et al.(4) have hypothesized that there is a close relationship between sub-clinical thromboendocarditis on the native valve and the early development of infective endocarditis on the implanted artificial valve. Others have observed that the organism presumed to be the cause of the prosthetic valve infective endocarditis (PVIE) was often different from the one isolated earlier as the presumed cause of the natural valve endocarditis(4a,4b). In the present study none of the 6 excised valves whose histology was available for re-examination showed signs of infection histologically. It is unfortunate that the bulk of the excised valves had evidently not been submitted for histopathological examination. Only 3 out of my 31 patients with infected prosthetic valves had clinically apparent pre-operative infective endocarditis. The diagnosis of prosthetic valve endocarditis had been made

clinically in the majority of our patients (87%).

Regarding the pathogenesis of fungal infection on heart valve prosthesis, Robboy and Kaiser(5) made the controversial suggestion that foci of infection start on patches of neo-endocardium on the sewing cloth of the valve prosthesis and that it is the neo-endocardium, rather than the cloth or metal of the prosthesis which is the important predisposing factor. The early development of post-operative infective endocarditis is recognized as a distinct hazard and unique clinical entity differing from non-surgical infective endocarditis in the following aspects(6) : (i) different organisms are involved ; (ii) the typical clinical picture of infective endocarditis is frequently lacking, and (iii) the fatality rate is unusually high.

INCIDENCE

The incidence of infective endocarditis after cardiac surgery varies in different series. The incidence is higher after surgery requiring cardio-pulomonary bypass than after "closed" intra-cardiac procedures(6). The incidence of infective endocarditis after prosthetic valvular replacement varies among different medical centres and is determined by many factors(7) including the underlying condition of the patient at the time of operation, the skill of the surgeon, the type of prosthesis used, the duration of cardio-pulmonary bypass, the sterility of the heart-lung machine and the operating theatre, the use of prophylactic antibiotics, the incidence of extra-cardiac post-operative infection and the length of the follow-up period after surgery. The incidence of early PVIE, defined as that occurring within 2 months after valve implantation, varies from 0 to 7.1% amongst different centres(2,8-27). The reported incidence of late PVIE for patients followed up for at least 6 months after surgery varies from 0 to 3.2% among different centres and the overall incidence of PVIE (all cases) varies from 0 - 9.5%, with an

average of 2.3%(7).

SOURCE OF THE ORGANISMS

Primary intra-operative contamination appears to be responsible for most post-operative endocarditis(6). Contamination of the heart-lung machine by diphtheroids and Pseudomonas(11) has resulted in endocarditis. The coagulase negative Staphylococcus, which was the commonest cause of PVIE in our patients, is ubiquitous in the air of operating rooms and on human skin. Ankeney(28) performed 1,555 intra-operative blood cultures during 383 open-heart operations and in 117 (7.5%) Staphylococcus albus was cultured ; 153 (9.8%) grew a diphtheroid bacillus and 29 (1.9%) were other micro-organisms. Most positive cultures were obtained from the primed pump and the suction line during bypass, when the pump and blood were most exposed to air. In addition to intra-operatice contamination, the organisms may be introduced by diagnostic cardiac catheterization, the prolonged use of intra-venous catheters, indwelling urinary catheters and contaminated blood. The valve prosthesis may become secondarily infected in all of the above circumstances. Finally, intrinsic contamination of the valve prosthesis itself is another potential source of infection(7). Porcine aortic valves from one manufacturer have been contaminated by Mycobacterium chelonei and at least 2 patients developed infective endocarditis(29,30).

INCREASED SUSCEPTIBILITY TO INFECTION

Many of the organisms producing PVIE are of a "low virulence". Increased susceptibility to infection may result from both local and general factors. Elek(31) showed that the presence of silk sutures potentiated Staphylococcus aureus infection of the skin up to 10,000-fold. Foreign material

placed within the heart increases the pathogenicity of bacteria and also makes infection difficult to eradicate by antimicrobial drugs. It has been suggested that cardio-pulmonary bypass may reduce the host's resistance to bacterial infections(6). The phagocytic activity of neutrophiles is depressed for as long as 18 days after open-heart surgery(32), but this was disputed by another study(33). Hairston(34) reported a significant lowering of IgG and total haemolytic complement during, and a few days after open-heart surgery and attributed this to denaturation of plasma proteins by the surface-polarizing forces at the blood-gas interface in oxygenators(35).

MICROBIOLOGY

The microbiology of PVIE is vastly different from that of natural valve infective endocarditis(7,36). The types of micro-organisms involved in my 31 patients with PVIE are characteristic of the findings of others in PVIE. Staphylococcus albus is the single most important cause of both early and late PVIE, accounting for 27.4% of the early caes and 22.9% of the late cases(7). This is in keeping with my finding that 23% of autopsied patients with PVIE were due to Staphylococcus albus. In the literature(37-43), Staphylococcus albus has been inculpated in anywhere from 6% to 35% of cases of PVIE. Staphylococcus aureus is an important cause of early PVIE, accounting for 19.2% of early cases and only 11.4% of late cases(7). It has been claimed that short-term peri-operative prophylaxis with a cephalosporin may prevent Staphylococcus aureus PVIE(18,27). Streptococci, which are the most important group of aetiological agents in infective endocarditis of natural valves, are not an important cause of PVIE, accounting for only about 7.5% of early cases(7) and were not encountered in my autopsy patients. However, Streptococci account for about 37% of late PVIE(7) and presumably have the same sources as in patients with infected natural heart valves.

According to Wilson et al.(44), gram-negative bacilli are the second leading cause of early-onset infections and are third in frequency among patients with late-onset PVIE. Gram-negative bacilli were the second most frequent pathogens in my 31 patients with fatal PVIE and accounted for 22% of the total. Gram-negative bacilli are a rare cause of infective endocarditis of natural valves except for intra-venous drug abusers(36). A wide variety of gram-negative bacilli have been isolated in PVIE, including species of Pseudomonas(10-12,45-47), Haemophilus(48-51), Escherichia coli(10-12,17), Alcaligenes faecalis(17) and Eikenella corrodens(52,53). Others include members of the genera Klebsiella(54), Serratia(9,54-57), Enterobacter(10,11,17), Proteus(10,17,54), and Hafnia(12). Other miscellaneous bacteria documented as causing PVIE include various species of diphtheroids(11,23,25,54,58), Actinobacillus actinomycetemcomitans(59), Nocardia asteroides(60), Neisseria species(61-63), Mycobacterium chelonei(64,65), Brucella(66), Bacillus cereus(67), Kingella kingae(68,69), Q Fever(70), and Listeria monocytogenes(71-73).

Fungal infections, which comprised 16% of my cases, are said by Watanakunakorn(7) to be responsible for 9.6% and 4.3% of the early and late cases, respectively. Fungal endocarditis following heart operations was first reported by Koelle and Pastor(74) in 1956, and by 1975 more than 120 cases had been reported in the English literature(75). Norenberg et al.(75) reported a 13-20% incidence of fungal endocarditis following cardiac operations. Candida albicans plus other Candida species are important causes of PVIE(14,21,22,24,46,54,76-81). Aspergillus is reported to be the next most important cause of fungal PVIE(7,14,45,54,79,82,83). Other fungi causing PVIE include Histoplasma capsulatum(84,85), Cryptococcus neoformans(79), Mucor(86), Paecilomyces(87-90), Penicillium notatum(91,92), and Trichosporon cutaneum(93).

PATHOLOGY

Although many reports are available on patients with fatal infective endocarditis of natural cardiac valves, there is limited information on the morphology of PVIE(94). Robinson et al.(95) reported on 16 autopsied patients with PVIE included in a larger series of patients with natural valve endocarditis, but gave no morphological details. PVIE may cause either obstruction or incompetence of the prosthesis(54,96). Madison et al.(49) described large peri-valvular abscesses which loosened the attachment of the prosthetic valve in each of 16 patients with PVIE. The early development of aortic regurgitation was a bad prognostic indicator. Arnett and Roberts(54) analysed 22 necropsy patients with PVIE ; as in my patients, the Staphylococcus was the most frequent infecting organism. In each of their patients the infection was located behind the site of attachment of the prosthesis to the native valve ring. Prosthetic obstruction by vegetations occurred more commonly with an infected mitral valve prosthesis than with aortic prostheses. Anderson et al.(96) recorded a clinicopathological study of 22 patients with PVIE. Prosthetic valve dysfunction led to death in 45% of their patients and embolic events in 23%. Ring infection, often believed to be universally present, and a contra-indication to surgery, was present in only 50% of their patients.

In a later paper Arnett and Roberts(97) described their further experience with infective endocarditis of both natural valves and heart valve substitutes. Other key references for PVIE are given as references(98-103) in the present work. A number of papers deal with general(104-106), clinico-pathological(107-109) or experimental aspects(110,111) of PVIE. Other authors address specific aspects of PVIE, including fatal obstruction to left ventricular inflow(112), rupture of mycotic aneurysms(113), embolism(114), bioprosthetic endocarditis(115-119), or surgical management of

prosthetic valve endocarditis(120-126). According to Schoen et al.(127), there is no apparent relationship to specific prosthetic valve type or design with respect to incidence or organisms. In most studies, the aortic site is involved more often than the mitral. Infection occurs within the first two months post-operatively (early onset) in approximately one-third to one-half of cases and later in the course (late onset) in the remainder. They state that the mortality rate is high, about 60% overall, being significantly higher for the early infection (73%) than for the late (45%). Since biomaterials themselves do not support the growth of infective organisms, the potentiation of infection by foreign bodies must involve an as yet poorly understood interaction of local physical and biological factors. A promising approach to prevention of PVIE is the incorporation of antibiotic into the valve prosthesis, to be slowly released during function(128).

E.SMALL CORONARY ARTERIAL DISEASE IN PATIENTS WITH IMPLANTED HEART VALVE PROSTHESES

The small coronary arteries (SCA) are often equated with intramyocardial coronary arteries. James(1) has pointed out that the two are not necessarily synonomous, since it is not unusual for a significant segment of a large coronary artery to course some distance within the myocardium. Conversely, most of the right ventricular small coronary branches lie in the epicardium and penetrate only a short distance into the myocardium. In the left ventricle the small coronary arteries are distributed throughout the myocardium and may also be seen in the epicardium. The small coronary arteries are important because they include important anastomoses, supply the conduction tissues, and may be involved by occlusive lesions in a variety of systemic diseases(2). In the present study the small coronary arteries are defined as those with a diameter of less than 1 mm.

Twenty-seven out of the 275 patients (18.6%) with valvular prostheses showed small coronary arterial abnormalities. Table 17.10 gives data regarding small coronary arterial disease in patients with valvular prostheses and 3 groups of control patients. It will be observed that the great majority of the small arteries in all 3 groups of patients examined showed no significant abnormality. Organized thromboemboli (eccentric intimal thickening) and concentric intimal fibrous thickening were the commonest abnormalities observed in SCA of patients with prostheses, being present in 2.7% and 2.3% of arteries respectively. However, the incidence of thromboemboli in patients with valvular prostheses did not differ significantly from unoperated patients with healed post-rheumatic valvular heart disease. Oedema of the arterial media was a feature of 6.7% of arteries in patients with acute rheumatic pancarditis, but was a neglible finding in the other patient groups. Foreign body emboli within small coronary arteries was noted only in patients with implanted valvular prostheses. Table 17.11 indicates the nature of the emboli

encountered in the latter patients. Three patients had more than one type of embolus within the small coronary arteries.

TABLE 17.10 : SMALL CORONARY ARTERIAL DISEASE IN PATIENTS WITH VALVULAR PROSTHESES AND IN 3 GROUPS OF CONTROL PATIENTS

	PTS.WITH PROSTHESES	RHEUMATIC FEVER ACTIVE	RHEUMATIC FEVER HEALED	ROUTINE AUTOPSY PTS
No. of PATIENTS	275	13	26	20
No. of ARTERIES	11261	676	1008	758
NORMAL	90.8%	85.9%	86.6%	96.6%
MEDIAL OEDEMA	0.2%	6.7%	0.6%	0.4%
LONGITUDINAL SMCs	0.1%	1.9%	1.1%	0.5%
MEDIAL HYPERTROPHY	0.9%	1.8%	1.8%	1.1%
INTIMAL FIBROSIS	2.3%	1.2%	1.6%	0.1%
ELASTIFICATION	NIL	NIL	2.6%	NIL
LOSS OF MURAL DEMARCATION	1.1%	0.7%	1.6%	0.1%
FRESH THROMBOEMBOLI	1.4%	0.6%	1.5%	0.5%
ORGANIZED THROMBOEMBOLI	2.7%	0.9%	2.4%	0.4%
FOREIGN BODY EMBOLI	0.5%	NIL	NIL	NIL
ARTERITIS	NIL	0.3%	0.2%	NIL

TABLE 17.11 : TYPES OF SMALL CORONARY ARTERIAL EMBOLI IN 275 PATIENTS WITH IMPLANTED CARDIAC VALVULAR PROSTHESES

TYPE OF EMBOLUS	No. of PTS.
THROMBOEMBOLUS	
FRESH	11
ORGANIZED	8
CALCIUM	4
ATHEROMATOUS	1
FOREIGN BODY	
SILICONE	2
FIBRES (? TEFLON)	2
UNIDENTIFIED	1
	TOTAL = 29

As regards the types of prostheses implanted in the patients with SCA disease, the University of Cape Town prosthesis (Table 17.12) showed the highest incidence of thromboembolism and concentric intimal thickening. It showed a much higher incidence of emboli than did the other types of prostheses listed in Table 17.12 (p less than 0.025) and an even more significantly greater occurrence of concentric intimal thickening (p less than 0.0025). The Starr-Edwards prosthesis also showed a greater (p less than 0.01) incidence of small coronary arterial embolism than did the other types of valves listed in Table 17.12 (excluding the University of Cape Town valve prosthesis). Patients with isolated UCT aortic valve prostheses(13) showed a 35% incidence of SCA abnormalities. The most frequent changes noted were intimal fibrous thickening (25%), medial hypertrophy (7.5%) and thromboembolism (17.5%).

TABLE 17.12 : TYPES OF CARDIAC PROSTHETIC VALVES PRESENT IN PATIENTS WITH CERTAIN TYPES OF SMALL CORONARY ARTERIAL DISEASE

VALVE TYPE	EMBOLI (%)	THICKENED INTIMA (%)
UNIVERSITY OF CAPE TOWN	14 (5.1)*	15 (5.5)**
CARPENTIER-EDWARDS	2 (0.7)	3 (1.1)
STARR-EDWARDS	6 (2.2)	-
MIXED	-	4 (1.5)
LILLEHEI-KASTER	2 (0.7)	-
HANCOCK	1 (0.4)	-
BJORK-SHILEY	-	1 (0.4)
St. JUDE MEDICAL	-	2 (0.7)

* p less than 0.025

** p less than 0.0025

COMMENT

It is apparent that small coronary arterial disease is not a major problem in patients with prosthetic heart valves. Only 29 out of the 275 patients (10.6%) with implanted valvular prostheses studied showed evidence of embolism in these small vessels. The incidence of thromboembolism did not differ significantly from that noted in patients with rheumatic fever or routine autopsy controls. Abernathy and Willis(3) stress that rheumatic heart disease is a thromboembolic disease in its own right. Foreign body emboli were confined to patients with prosthetic valves and increased elastification of SCA was only encountered in unoperated patients with chronic rheumatic-type valvular heart disease. For some unknown reason, this change was not noted in the vessels of the patients with prostheses, most of whom had had similar pre-operative valvular lesions. Patients with healed rheumatic fever (mitral valve disease without Aschoff bodies) showed less medial oedema than those with Aschoff bodies. Grismer et al.(4) suggested that chronic occlusive rheumatic vasculitis may be a cause of the low output syndrome leading to mortality following corrective heart surgery for mitral valvular defects. Such an eventuality was a rare occurrence in the present study - one of our patients with this complication is illustrated as Figure 9.6 in a standard text(2).

While calcium embolism may accompany surgical resection of calcified left-sided heart valves(5), Wigle(6) showed that calcific emboli could arise de novo from a heavily calcified, ulcerated aortic valve and also from a calcified valve after mitral valvotomy. There is a high risk of calcium microemboli in patients with a heavily calcified valve annulus who undergo valve replacement, since debridement of the calcified annular tissue is difficult(2). The use of microfilters in the bypass circuit has reduced the incidence of this complication. Other

forms of foreign body microemboli related to cardiac surgery include cholesterol, suture material, silicone from the oxygenator pump(7), Teflon from prosthetic valves(8,9), and Dacron from the worn cloth covering of prosthetic valves. A diagnosis of cloth fibre emboli rather than thromboemboli may be favoured by the clinical manifestation of recurrent systemic arterial embolization more than 4 years after valve replacement and despite adequate anticoagulation(10). Platelet aggregates formed in the pump oxygenator may lodge as microemboli in small coronary arteries of patients undergoing cardiopulmonary bypass. Bone marrow emboli or adipose tissue as well as air embolization are also occasionally encountered.

In the present series 19% of patients with cardiac valvular prostheses had small coronary arterial disease. Roberts et al.(11) found embolic material in the intramural coronary arteries of 9% of patients dying after heart valve replacement. Silver(12) found foreign body emboli in about 10% of patients who died late after cardiac valve replacement. Many such emboli appeared as granulomata related to and involving SCA, but without an obvious associated foreign body. The number of emboli and granulomata found increase and become more widespread in distribution if there has been wear of the prosthesis.

F. PATHOLOGY OF THE MAJOR CORONARY ARTERIES

The 275 patients with implanted cardiac valvular prostheses showed the following coronary arterial pathology :

THROMBOEMBOLISM

Thromboemboli were encountered within the coronary arteries of 17 patients ; myocardial infarction was detected macroscopically in only 6 out of these 17 hearts. In 16 patients the thromboemboli were lodged within epicardial coronary arteries, but in one patient a thromboembolus was found within a large septal perforator branch of the left anterior descending coronary artery. The patient died suddenly and unexpectedly.

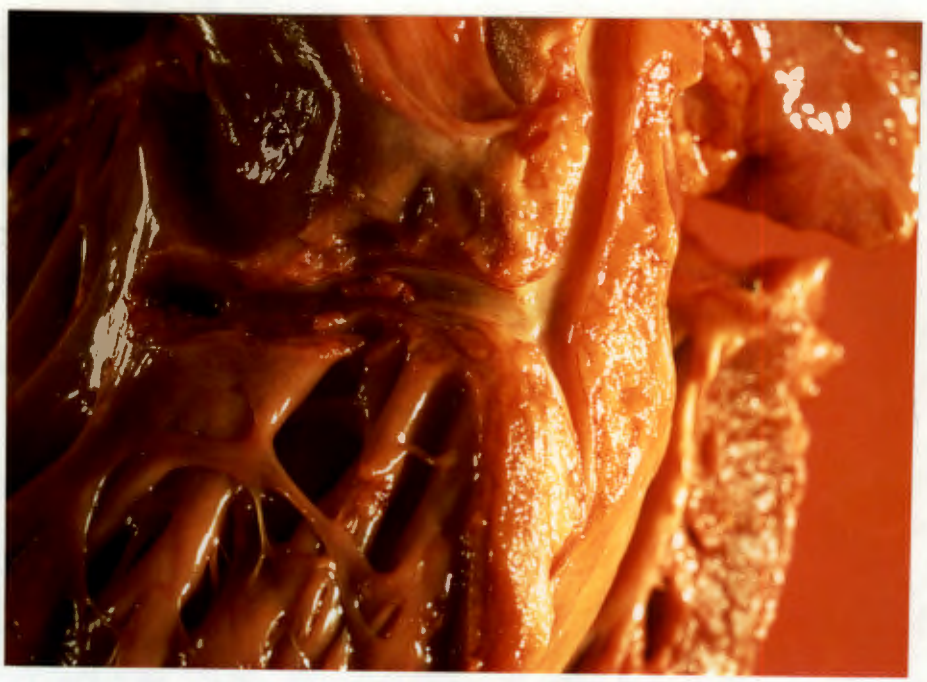

Figure 17.6 : Thromboembolus lies within a septal perforator branch of left anterior descending coronary artery. Such arteries are seldom examined at autopsy and, if the embolus had not been discovered, the patient's sudden death might have been attributed to arrhythmia.

SEVERE ATHEROSCLEROSIS

Seventeen patients (6%) had severe coronary arterial atherosclerosis, which was defined as 75% or more reduction in luminal cross-sectional area of one or more of the major coronary arteries. Seven of these patients underwent saphenous vein coronary arterial bypass grafting at the same time as the valve surgery. Coronary atherosclerosis per se was a principal cause of death in only 3 of these patients.

MISCELLANEOUS CONDITIONS

Miscellaneous conditions were noted in 10 patients. Two patients showed surgical sutures penetrating their left circumflex coronary artery. Both of these arteries occupied a deeper than usual (intra-myocardial) situation at the site of involvement by the sewing sutures. I also encountered a patient who had a congenital early bifurcation of the left main coronary artery. This resulted in the coronary perfusion cannula entering the left anterior descending branch only, with occlusion of the non-perfused left circumflex coronary artery.

Two patients with coronary arterial ostial stenosis both had coronary arterial bypass grafts (CABG) performed using the saphenous vein. One patient was known to suffer from syphilis, but the aetiology of the ostial stenosis was uncertain in the other, and was probably due to atherosclerosis. In a third patient a Lillehei-Kaster aortic valve prosthesis had been inserted in such a way so as to cause partial obstruction of both coronary arterial ostia ; the patient did not survive the operation. Another patient had redundant suture material from the sewing ring of an aortic valve prosthesis protruding into the left coronary arterial ostium, but no significant obstruction resulted.

Three patients showed coronary arterial dissection ; in

one patient with aortic medionecrosis the coronary arterial involvement was due to extension of an aortic dissecting aneurysm, whereas in the other patient the coronary dissection was iatrogenic having occurred during coronary angiography. The dissection in the third patient was a complication of CABG for atherosclerotic coronary arterial disease.

COMMENT

Significant coronary arterial disease was present in only 6% of the patients in the present study compared to 22% of the patients reported by Schoen et al.(1) from America. This difference may be related mainly to differences in the population undergoing operation in the two centres (Cape Town and Houston). A large number of our patients were blacks, coloureds or young whites with chronic rheumatic valvular heart disease in whom atherosclerosis is infrequent. The Houston patients were generally older and rheumatic fever was probably a less common aetiological factor. Roberts and Hammer(2) noted severe atherosclerotic coronary arterial narrowing in 13 out of 46 patients with tilting disc prostheses and it was a major cause of death in 5 out of 33 early post-operative deaths.

Forty-one percent of our patients with severe coronary arterial atherosclerotic narrowing underwent CABG at the time of heart valve replacement. Operations for replacement of the aortic valve combined with coronary revascularization are time consuming and stress the strategies for protecting the myocardium. Lytle et al.(3) found that in-hospital mortality in such cases was increased by female sex, aortic insufficiency, and advanced age, whereas cardioplegia reduced it. The late survival rate was unfavourably influenced by the presence of moderately or severely impaired left ventricular function and double-vessel coronary arterial disease. The rate was enhanced for patients in the age-group from 50 to 59 years old, and was not influenced by the method of myocardial

protection.

Unless dye contrast methods are used, significant lesions may be missed in the larger penetrating branches of the major coronary arteries. This is illustrated by the patient described above in whom a thromboembolus was discovered in a large septal perforator branch of the anterior descending coronary artery. The patient's sudden, unexpected death would have been attributed to an arrhythmia if the thromboembolus had not been detected. Coronary arterial dissection is a recognized complication of CABG(4) and may result from surgical damage to the posterior wall of the vessel at the site of incision into the coronary artery (anastomotic site).

G. STATE OF THE MYOCARDIUM IN PATIENTS WITH PROSTHETIC HEART VALVES

1. HEART WEIGHTS

Table 17.13 indicates the mean heart weights in early (group 1) and late (group 2) survivors following heart valve replacement and also compares the heart weights of patients with and without the clinical features of myocardial pump failure. Early and late survivors showed no significant difference in mean heart weights. However, patients dying with myocardial failure had significantly heavier hearts than those without failure (p less than 0.05).

TABLE 17.13 : MEAN HEART WEIGHTS IN PATIENTS WITH IMPLANTED PROSTHETIC HEART VALVES WITH REFERENCE TO DURATION OF POST-OPERATIVE SURVIVAL AND CARDIAC FAILURE

PATIENTS	HEART WTS.(g),MEAN,(SD)
GROUP 1 (N=114)	646 (203)
GROUP 2 (N=121)	660 (226)
PTS WITHOUT FAILURE (N=207)	635 (208)*
PTS WITH FAILURE (N=28)	732 (202)*

* p less than 0.05

2. MYOCARDIAL NECROSIS

COAGULATIVE NECROSIS was observed naked eye in 20 patients (7%) ; it was transmural in 6, sub-endocardial in 3

and a mixture of these two patterns in 11 patients. CIRCUMFERENTIAL HAEMORRHAGIC SUB-ENDOCARDIAL INFARCTION(1,2) of the left ventricle was observed in an additional group of 9 patients, most of whom had a low cardiac output and survived less than one day post-operatively. All of these heart also showed concentric hypertrophy of the left ventricle with sub-endocardial focal replacement fibrosis and the heart weights ranged from 430 to 1172 grams, with a mean of 678 grams (S.D.= 312). All of the patients with subendocardial necrosis had undergone aortic valve replacement and two patients underwent double valve replacement. Two patients had coronary arterial bypass grafts performed for severe atherosclerotic coronary arterial disease, with bypass times of 6 and 9 hours respectively. Only one out of the 9 patients was operated upon after 1977, i.e. after the institution of cold cardioplegic myocardial protection during cardiopulmonary bypass.

The "STONE HEART" SYNDROME(3) was encountered in three patients, all of whom were operated upon before 1977. They showed massively hypertrophied hearts with severe concentric hypertrophy of the left ventricle. All three patients did not survive the operation.

Scores for the 3 morphological forms of myocardial necrosis evaluated histologically, namely COAGULATIVE NECROSIS, CONTRACTION BAND NECROSIS and MYOCYTOLYSIS(see Methodology), are given in Tables 17.14-17.16. No significant difference was found in the necrosis scores in comparing the total groups of 275 patients with valvular prostheses and the 75 control patients with non-operated valvular heart disease. However, patients with Starr-Edwards prostheses showed significantly more myocardial necrosis (Table 17.14) than was seen in patients with other types of implanted prosthetic heart valves and this was most marked for coagulative necrosis in patients with Starr-Edwards mitral prostheses.

TABLE 17.14 : MYOCARDIAL NECROSIS IN AUTOPSIED PATIENTS WITH VARIOUS TYPES OF PROSTHETIC HEART VALVES AND IN NON-OPERATED CONTROLS WITH VALVULAR DISEASE, MEDIAN (RANGE).

PTS. WITH PROSTHESES	TYPE OF NECROSIS (SCORED 0-3)		
	COAGULATIVE	CONTRACTION BAND	MYOCYTOLYSIS
UCT-A	0 (0-3)	0 (0-1)	0 (0-1)
UCT-M	0 (0-1)	0 (0-1)	0 (0-3)
UCT-MULT	0 (0-3)	0 (0)	0 (0-2)
S-E-MVR	0 (0-3)a	0 (0-2)	0 (0-3)
S-E-AVR	0 (0-2)	0 (0-2)b	1 (0-2)c
B-S	0 (0-3)	0 (0)	0 (0)
SJM	0 (0-3)	0 (0)	0 (0-3)
LILL	0 (0-3)	0 (0-1)	0 (0-1)
HAN	0 (0-3)	0 (0-1)	0 (0-2)
C-E	0 (0-3)	0 (0-3)	0 (0-3)
COMBINED PTS (N=275)	0 (0-3)	0 (0-3)	0 (0-3)
COMBINED CONTROLS (N=85)	0 (0-3)	0 (0-1)	0 (0-1)

The differences are not significant except where indicated. a = $p<0.001$; b and c both = $p<0.05$.

TABLE 17.15 : MYOCARDIAL NECROSIS IN PATIENTS WITH UCT AORTIC PROSTHESES AND IN NON-OPERATED CONTROLS WITH AORTIC VALVULAR DISEASE, MEDIAN (RANGE).

FUNCTIONAL ABNORMALITY	PTS.	MORPHOLOGICAL GRADING (0-3) OF 3 FORMS OF NECROSIS		
		COAGULATIVE	CONTRACTION BAND	MYOCYTOLYSIS
AS	PTS. (N-6)	1 (0-3)	0 (0)	0 (0)
	CONTROLS(N=23)	0 (0-3)	0 (0)	0 (0-1)
AI	PTS. (N=18)	0 (0-1)	0 (0-1)	0 (0-1)
	CONTROLS(N=17)	0 (0-3)	0 (0-1)	0 (0-1)
AS/AI	PTS. (N=17)	0 (0-3)	0 (0)	0 (0-1)
	CONTROLS(N=14)	0 (0-3)	0 (0-1)	1 (0-1)

The differences are not significant.

AS=aortic stenosis;AI=aortic incompetence.

TABLE 17.16 : MYOCARDIAL NECROSIS IN PATIENTS WITH STARR-EDWARDS MITRAL PROSTHESES AND IN NON-OPERATED CONTROL PATIENTS WITH MITRAL VALVULAR DISEASE, MEDIAN (RANGE).

FUNCTIONAL ABNORMALITY	PTS.	MORPHOLOGICAL GRADING (0-3) OF 3 FORMS OF NECROSIS		
		COAGULATIVE	CONTRACTION BAND	MYOCYTOLYSIS
MS	PTS.(N=9)	0 (0-2)	0 (0)	0 (0-1)
	CONTROLS(N=11)	0 (0-1)	0 (0)	0 (0-1)
MI	PTS.(N=6)	0 (0-2)	0 (0-1)	0 (0-3)
	CONTROLS(N=13)	0 (0)	0 (0)	0 (0)
MS/MI	PTS.(N=10)	1.5 (0-3)	0 (0-2)	0 (0-2)
	CONTROLS(N=7)	0 (0)	0 (0)	0 (0)

The differences are not significant

Table 17.17 compares the necrosis scores of two groups of early survivors after valve replacement who were divided according to the form of intra-operative myocardial protection that was used. The first group of 45 patients was treated with intra-operative coronary arterial perfusion with blood from the oxygenator-pump machine with separate perfusion of the two coronary arteries, individual monitoring of pressure and flow plus cooling of the beating heart to 32 degrees Centigrade. The second group of 42 patients received cold cardioplegic solution and the heart was cooled down to about 15 degrees Centigrade and arrested in diastole by potassium administration. It is apparent from Table 17.17 that the 3 forms of myocardial necrosis occurred with equal severity in the 2 groups of patients.

Another aspect that was investigated (Table 17.18) was the state of the myocardium in patients who received intermittent versus continuous coronary arterial perfusion with blood during cardiopulmonary bypass ; and a similar evaluation was performed for patients with regularly beating hearts versus those whose hearts fibrillated continuously during bypass. No significant differences were found. I also found that group 1 patients, (presumably with myocardial lesions related to inadequate operative myocardial protection amongst other factors), showed no significant difference in myocardial necrosis scores (Table 17.19) compared to group 2 patients (who should be less affected by operative factors, and more influenced by thromboembolism and infection).

Figure 17.7 : Concentric haemorrhagic necrosis of the left ventricle in a patient with a Starr-Edwards aortic valve prosthesis.

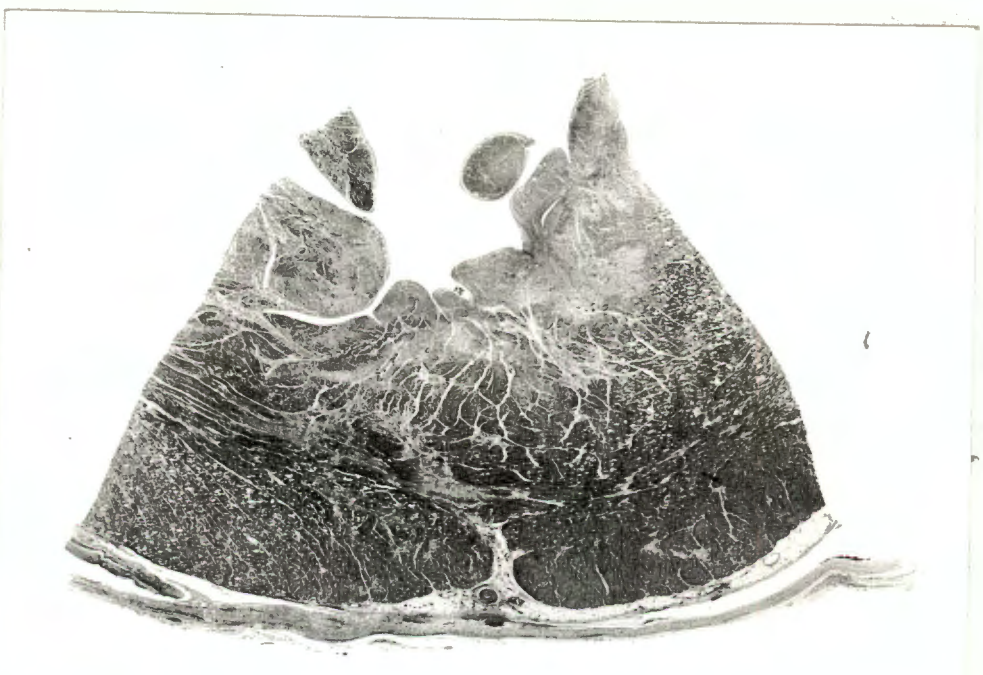

Figure 17.8 : Section of left ventricle shows sub-endocardial replacement fibrosis. Necrosis of adjacent myofibres is not apparent at this low power. (Haematoxylin-eosin, X 4).

TABLE 17.17 : MORPHOLOGICAL ASSESSMENT OF MYOCARDIAL NECROSIS IN EARLY SURVIVORS WITH 2 DIFFERENT TYPES OF INTRAOPERATIVE MYOCARDIAL PROTECTION, MEDIAN (RANGE)

MYOCARDIAL PROTECTION	TYPES OF NECROSIS (SCORED 0-3)		
	COAGULATIVE	CONTRACTION BAND	MYOCYTOLYSIS
ICPBH(N=45)	0 (0-3)	0 (0-3)	0 (0-2)
CCA (N=42)	0 (0-3)	0 (0-3)	0 (0-3)

The differences are not significant. ICPBH=intermittent coronary perfusion with blood and a beating heart. CCA=cold cardioplegic cardiac arrest.

TABLE 17.18 : MYOCARDIAL NECROSIS (SCORED 0-3) IN PATIENTS WITH DIFFERENT FORMS OF CORONARY ARTERIAL PERFUSION AND VENTRICULAR RHYTHM DURING CARDIOPULMONARY BYPASS, MEDIAN (RANGE).

		CORONARY PERFUSION		VENTRICULAR RHYTHM	
NECROSIS	PTS.	INTERMITTENT	CONTINUOUS	BEATING REGULARLY	FIBRILLATING
		(N=14)	(N=21)	(N=16)	(N=21)
	GRP 1	0 (0-2)	0 (0-1)	0 (0-2)	0 (0-2)
COAGULATIVE	GRP 2	0 (0-3)	0 (0-3)	0 (0-3)	0 (0-3)
	1+2	0 (0-3)	0 (0-3)	0 (0-3)	0 (0-3)
	GRP 1	0 (0)	0 (0)	0 (0)	0 (0)
CONTRACTION	GRP 2	0 (0)	0 (0)	0 (0)	0 (0)
BAND	1+2	0 (0)	0 (0)	0 (0)	0 (0)
	GRP 1	0 (0-1)	0 (0-1)	0 (0-1)	0 (0)
MYOCYTO-	GRP 2	0 (0-1)	0 (0)	0 (0)	0 (0)
LYSIS	1+2	0 (0-1)	0 (0-1)	0 (0-1)	0 (0)
No. of Pts. in Grp 1		6	12	8	10
No. of Pts. in Grp 2		8	9	8	11

The differences are not significant

3. MYOCARDIAL FIBROSIS

Twenty-one out of the 275 patients (8%) with implanted heart valve prostheses showed macroscopically recognizable sub-endocardial left ventricular fibrosis. Transmural fibrosis was observed naked eye in 8 patients (3%). Histological evidence of fibrosis was present in most patients. Morphometry showed no significant difference in the amount myocardial fibrous tissue in 275 patients with prostheses compared to 85 controls with native valvular heart disease (Table 17.20).

TABLE 17.20 : MORPHOMETRY OF MYOCARDIAL FIBROSIS IN PATIENTS WITH VALVULAR PROSTHESES AND IN NON-OPERATED CONTROLS WITH VALVULAR DISEASE, MEAN (STANDARD DEVIATION).

	MORPHOMETRY (%)
PATIENTS WITH VALVULAR PROSTHESES (N=275)	13.7 (13.4)
CONTROLS WITH VALVULAR DISEASE (N=85)	10.3 (10.0)

No significant difference is present

Morphological assessment of the 4 forms of myocardial fibrosis (replacement, interstitial, perivascular and plexiform) in patients with implanted prostheses and non-operated control patients revealed a significantly greater amounts of replacement and interstitial fibrosis in the combined group of patients with valvular prostheses (Table 17.21) ; no difference was found with regard to the other 2 types of fibrosis.

Group 2 patients with University of Cape Town valvular prostheses (Table 17.22) showed more replacement fibrosis than did the group 1 patients. Patients with pre-operative aortic

stenosis showed no difference from matched controls with regard to morphological grading of fibrosis and morphometry. Patients with pre-operative aortic incompetence and patients with mixed aortic valvular disease both showed no significant difference in morphological assessment of fibrosis from controls, but there was a significant difference for in morphometric score for fibrosis in general compared to controls (Table 17.23). A similar evaluation of patients with UCT mitral prostheses and non-operated controls with mitral valvular disease (Table 17.24) revealed greater degrees of all 4 forms of fibrosis in patients operated upon for mixed mitral stenosis and incompetence compared to controls. In patients with Starr-Edwards mitral valvular prosthesis (Table 17.25) those with pre-operative mitral stenosis as well as those with mixed mitral valvular disease also showed a greater amount of replacement fibrosis than controls.

TABLE 17.21 : MORPHOLOGICAL ASSESSMENT (SCORED 0-3) OF MYOCARDIAL FIBROSIS IN 275 PATIENTS WITH VALVULAR PROSTHESES AND IN 85 CONTROLS WITH NON-OPERATED NATURAL VALVULAR DISEASE, MEDIAN (RANGE).

	PATTERNS OF MYOCARDIAL FIBROSIS			
PATIENTS	REPLACEMENT	INTERSTITIAL	PERIVASCULAR	PLEXIFORM
PATIENTS WITH PROSTHESES (N=275)	1 (0-3)a	0 (0-3)b	0 (0-3)	0 (0-2)
UNOPERATED CONTROLS (N=85)	0 (0-3)a	0 (0-3)b	0 (0-3)	0 (0-2)

The differences are not significant except where indicated. a = $p < 0.001$; b = $p < 0.05$

MYOCARDIUM

TABLE 17.22 : MYOCARDIAL FIBROSIS (SCORED 0-3) IN EARLY (GROUP 1) AND LATE (GROUP 2) SURVIVING PATIENTS WITH UCT AORTIC VALVE PROSTHESES.

	GRADING OF FIBROSIS, MEDIAN (RANGE)				MORPHOMETRY (%) MEAN (S.D.)
	REPLACEMENT	INTERSTITIAL	PERIVASCULAR	PLEXIFORM	
GROUP 1 (N=20)	1 (0-3)a	1 (0-3)	1 (0-3)	0 (0-2)	21.8 (18.7)
GROUP 2 (N=21)	1.5 (0-3)a	0 (0-2)	0 (0-2)	0 (0-1)	24.4 (13.8)

The differences are not significant except where indicated. a = $p < 0.05$

TABLE 17.23 : MYOCARDIAL FIBROSIS IN PATIENTS WITH UCT AORTIC VALVE PROSTHESES AND IN NON-OPERATED CONTROLS WITH AORTIC VALVULAR DISEASE.

VALVE LESION, PTS.	MORPHOLOGICAL GRADING (0-3), MEDIAN (RANGE)				MORPHOMETRIC SCORE (%)
	REPLACEMENT	INTERSTITIAL	PERIVASCULAR	PLEXIFORM	MEAN, (S.D.)
AS PTS(N=6)	1 (0-3)	1 (0-2)	0 (0-2)	0 (0)	16.1 (10.6)
CONTROLS (N=25)	0.5 (0-3)	0 (0-3)	0 (0-2)	0 (0-1)	20.6 (18.5)
AI PTS(N=18)	1 (0-3)	1 (0-2)	1 (0-2)	0 (0-1)	19.9 (14.0)a
CONTROLS (N=17)	0 (0-2)	1 (0-2)	1 (0-2)	0 (0-1)	5.5 (5.1)a
AS/AI PTS (N=17)	1.5 (0-3)	1 (0-3)	0.5 (0-3)	0 (0-2)	28.1 (18.1)b
CONTROLS (N=12)	1 (0-3)	0.5 (0-2)	0.8 (0-1)	0 (0-1)	10.7 (11.8)b

The differences are not significant except where indicated. a = $p < 0.001$; b = $p < 0.05$.

TABLE 17.24 : MYOCARDIAL FIBROSIS IN PATIENTS WITH UCT MITRAL VALVULAR PROSTHESES AND IN NON-OPERATED CONTROLS WITH MITRAL VALVULAR DISEASE.

FUNCTIONAL ABNORMALITY & PTS.	MORPHOLOGICAL GRADING (0-3) OF FIBROSIS, MEDIAN (RANGE)				MORPHOMETRY SCORE (%)
	REPLACEMENT	INTERSTITIAL	PERIVASCULAR	PLEXIFORM	MEAN (S.D.)
PTS.(N=6) MS	0 (0-3)	0 (0-2)	0 (0-1)	0 (0)	18.1 (22.0)
CONTROLS (N=11)	0 (0-3)	0 (0-2)	0 (0-2)	0 (0-1)	10.6 (10.9)
PTS.(N=6) MI	0 (0-1)	0 (0-2)	0.5 (0-2)	0 (0-1)	4.7 (4.0)
CONTROLS (N=13)	0 (0-2)	0 (0-2)	0 (0-1)	0 (0-1)	8.2 (9.2)
PTS.(N=14) MS/MI	1 (0-3)a	0.3 (0-2)b	0.5 (0-1)c	0 (0-1)d	9.9 (5.9)
CONTROLS (N=7)	0 (0-1)a	0 (0-1)b	1 (0-1)c	0 (0)d	7.2 (6.6)

The differences are not significant except where indicated. a = $p < 0.001$; b = $p < 0.01$; c = $p < 0.05$; d = $p < 0.01$

TABLE 17.25 : MYOCARDIAL FIBROSIS IN PATIENTS WITH STARR-EDWARDS MITRAL PROSTHESES AND IN NON-OPERATED CONTROLS WITH MITRAL VALVULAR DISEASE.

FUNCTIONAL ABNORMALITY & PTS.	MORPHOLOGICAL GRADING (0-3) OF FIBROSIS, MEDIAN (RANGE)				MORPHOMETRY SCORE (%) MEAN (S.D.)
	REPLACEMENT	INTERSTITIAL	PERIVASCULAR	PLEXIFORM	
PTS.(N=8) MS	1.5 (0-3)a	0 (0-2)	0 (0-1)	0 (0)	13.4 (11.4)
CONTROLS (N=11)	0 (0-3)a	0 (0-1)	0 (0-2)	0 (0-1)	10.6 (10.9)
PTS.(N=4) MI	1 (0-2)	0 (0-1)	0.5 (0-2)	0 (0)	7.5 (7.6)
CONTROLS (N=13)	0 (0-2)	0 (0-2)	0 (0-1)	0 (0-1)	8.2 (9.2)
PTS.(N=12) MS/MI	1 (0-2)b	0 (0-1)	0 (0)	0 (0-1)	5.7 (6.6)
CONTROLS (N=7)	0 (0-1)b	0 (0-1)	1 (0-1)	0 (0)	7.2 (6.6)

The differences are not significant except where indicated. a = $p < 0.02$; b = $p < 0.001$

valves whose function they aim to replace. This obstructive effect may be a factor in the persistence of cardiac hypertrophy post-operatively, especially with aortic valve replacement. It is clearly not the sole explanation for the persistent hypertrophy, since persistent left ventricular hypertrophy was also observed in hearts with isolated mitral valvular replacement for mitral incompetence. Myocardial fibrosis due to rheumatic fever or ischaemia may also play a role in this regard.

NECROSIS

Necrosis of the myocardium was more severe (Chi-square evaluation, Table 17.14) in patients with Starr-Edwards valvular prostheses compared to patients with other types of necrosis. The reason for this is unknown. The combined group of 275 patients with implanted prostheses failed to show more necrosis than the 85 control patients with unoperated valvular disease. The control patients had a predominance of rheumatic heart disease and also probably suffered from reduced myocardial perfusion due to cardiac failure and coronary thromboembolism.

In view of reports(6-11) that cold cardioplegic cardiac arrest is a superior means of protecting the myocardium during cardiopulmonary bypass, it is surprising that this study found no significant difference with regard myocardial necrosis scores (Table 17.17) in the 2 study groups with and without cold cardioplegia. However, it should be noted that only one autopsied patient with a reperfusion-type, circumferential, haemorrhagic, sub-endocardial left ventricular myocardial infarction was encountered following the introduction of cold cardioplegic cardiac protection at our institution in 1977, compared to 8 autopsy cases prior to that date. Most of these patients had a low cardiac output and died within the first 24 hours post-operatively. Cardioplegia may thus play an important role in preventing this specific form of myocardial

necrosis. A retrospective, non-randomised study comparing intermittent ischaemic cardiac arrest with cold cardioplegia showed a similar incidence of peri-operative myocardial damage in the 2 groups of patients(12). A different, randomised study(13) suggested that cardioplegia confers greater protection.

All of our patients with reperfusion-type haemorrhagic infarcts of the left ventricle showed severe post-operative myocardial failure. Like other reported cases(1,2) our patients had undergone either aortic valve or double valve replacement. Gotlieb et al.(1) describe 5 major histological changes which probably represent the sequential evolution of concentric haemorrhagic necrosis of the myocardium after cardiopulmonary bypass. These were contraction bands, sub-endocardial haemorrhages, coagulative necrosis, healing by granulation tissue and fibrosis. The location of the lesion coincided with the vulnerable region of the microcirculation.

Patients with severe hypertrophy represent a high-risk group in cardiac surgery because of their reduced tolerance to induced myocardial ischaemia during cardiopulmonary bypass(14). The existence of a post-operative low-cardiac-output syndrome has been denied by some, and other have referred to it by descriptive terms such as "post-operative heart failure"(15-20). A source of difficulty in identifying the syndrome clinically arises from inclusion within it of patients with a variety of intra-cardiac mechanical problems, such as valve prostheses of improper size, leakage around a valve, and subaortic outflow tract obstruction by mitral prostheses(15). Some(21) have even included patients with reduced cardiac output due to hypovolaemia and pericardial tamponade.

Early reports(11,22,23) of the low-cardiac-output syndrome made no mention of myocardial necrosis. Then, in 1967 Taber et al.(15) implicated left ventricular myocardial necrosis as a cause of fatal post-operative myocardial failure. They(15) suggest that only low cardiac output due to

primary myocardial factors should be included in the syndrome. In the same year, Najafi et al.(4,24) showed that acute diffuse subendocardial myocardial infarction was frequent in patients dying soon after valve replacement and they suggested that it was related to intra-operative management of the myocardium. Later experience with coronary-artery-bypass grafting(25-27) led cardiologists and cardiac surgeons to observe even more clearly that current techniques of myocardial protection were inadequate. At about the same time, a rare and extreme form of ischaemic damage, "stone heart"(3,28) was recognized as essentially a massive myocardial infarction(29,30).

Ischaemic myocardial contracture ("stone heart") is one of several forms of myocardial failure that may result from myocardial ischaemia during cardioplumonary bypass. Cooley et al.(31) list the following potential myocardial causes of post-operative heart failure : subendocardial haemorrhagic contraction band necrosis, ordinary myocardial infarction, ultrastructural damage, ventricular arrhythmia and a flaccid, non-contractile heart as causes of pump failure after bypass.

In 1972, Cooley et al.(3) first reported the "stone heart" syndrome. In its fully developed form it represents an uncommon complication of ischaemic cardiac arrest during cardiopulmonary bypass, is analogous to rigor mortis in skeletal muscle(30,32) and results from ATP-depletion rigor in the ischaemic myocardium. According to Silver(5) it may be produced reproducibly in several animal species by maintaining global ischaemia in a controlled normothermic setting and without a need for reperfusion. It may also be prevented under experimental conditions by moderate hypothermia(33). Isolated hearts given a calcium-free perfusion followed by a normocalcaemic reperfusion develop the ischaemic contracture in less than 5 minutes(34). This calcium paradox effect is temperature-dependent and can also be prevented by hypothermia(34). The heart is firm to palpation, the ventricular cavity is minuscule (concentric hypertrophy) and

no cardiac output can be obtained on manual massage.

Whilst Cooley et al.(31) stress that severe myocardial fibrosis and hypertrophy are usually present and recognizable myocardial necrosis is absent in most cases, others(14,35) report that, as in our patients, the pathological basis of the stone heart syndrome is the presence of massive myocardial contraction band necrosis. This may go on to myocytolysis(36). Hutchins et al.(35) confirmed that the stone heart syndrome appears to be simply the manifestations produced by contraction band necrosis in a severely hypertrophied heart. The condition may occur even with normal coronary arteries. Ultrastructural examination of the stone heart myocardium showed features of an accelerated form of ischaemic injury(29). Others(37-40) also report on the ultrastructural alterations that may accompany ischaemia and reperfusion in human hearts during cardiac surgery. It has been suggested(41) that direct mechanical trauma to the endocardium may play a role in the development of sub-endocardial haemorrhagic necrosis.

In my patients there was no difference in necrosis scores between patients who received intermittent versus continuous coronary perfusion during cardiopulmonary bypass. This finding concurs with the experience of Kirklin et al(11) who state that intermittent coronary arterial perfusion induces at least as much myocardial-cell death as does direct coronary perfusion. Balibrea et al.(42) reported that both intermittent and continuous coronary perfusion were effective in preventing anoxic damage during bypass.

Several authors(43,44) describe deleterious effects if the heart is allowed to fibrillate during cardiopulmonary bypass ; there is an association with greater myocardial ischaemia and a higher early post-operative mortality rate. The present study revealed that beating hearts showed no significant difference with regard to necrosis compared to hearts that fibrillated during bypass.

Levitsky and Feinberg(45) review the problem of

intra-operative myocardial protection during cardiopulmonary bypass, and they discuss the following therapeutic approaches : (i) normothermic ischaemic arrest ; (ii) direct coronary arterial perfusion ; (iii) intermittent coronary perfusion ; (iv) induced electrical fibrillation of the heart ; (v) systemic hypothermia ; (vi) topical hypothermia ; (vii) potassium-induced cardioplegia ; and (viii) intra-aortic perfusion. Cardioplegia (induction of electromechanical arrest) as an aid to intracardiac exposure during cardiac operations was introduced by Melrose et al.(46) in 1955. Bretschneider et al.(47) performed important early work in this regard. Several groups then showed that cardioplegia with myocardial cooling provided better myocardial protection than either procedure alone(7,8,48,49). Since then a voluminous literature on cardioplegia has developed(50-54), most of which fall outside of the scope of this work.

FIBROSIS

Myocardial fibrosis was detected much more commonly in histological sections than was apparent to the naked eye. Morhometry (point-counting) revealed no significant difference between patients with prostheses and non-operated controls with regard to the amount of myocardial fibrosis. Assessment of fibrosis using a more subjective morphological scoring system showed replacement and interstitial fibrosis more commonly in patients with prostheses compared to the controls (Table 17.21). Replacement fibrosis was more extensive in late compared to to early survivors with UCT aortic valvular prostheses (Table 17.22). Comparison of functional classes of valvular disease revealed that patients with pre-operative aortic incompetence or mixed aortic valvular disease showed higher morphometric scores for fibrosis (17.23) compared to controls with similar valvular dysfunction. Patients with UCT valves inserted for mixed mitral valvular disease showed more replacement, interstitial and perivascular fibrosis than was

seen in the controls (17.24). Morphometry showed no difference between the same groups. Those with Starr-Edwards mitral prostheses appeared to have increased replacement fibrosis in patients who had mitral stenosis or mixed mitral valvular disease pre-operatively, but morphometry showed no significant differences (Table 17.25).

The fibrosis observed in the myocardium of patients with implanted heart valves may have a multifactorial aetiology, including pre-existing rheumatic or ischaemic heart disease, bypass-induced necrosis(5), thromboembolism (due to rheumatic fever or from thrombi situated upon the prosthetic valve), and poor subendocardial perfusion due to heart failure. The general conclusion from the present study is that patients with implanted prostheses show a similar degree of myocardial fibrosis to that seen in non-operated controls with valvular disease.

H. POST-PERFUSION LUNG.

Post-perfusion lung is the name given to the "adult" repiratory distress syndrome that may occur following heart valve replacement(1), particularly if there is a prolonged bypass period. The pathogenesis of the condition is obscure ; suggested causes include platelet and leucocytic microemboli in the pulmonary micro-circulation with possible release of biologically active substances and circulatory obstruction. Resultant changes in surfactant levels may also play a role(2). In this work I encountered 4 autopsied patients who had had features during life consistent with "post-perfusion lung", which is characterized clinically by dyspnoea, arterial hypoxaemia with an increased alveolar-arterial oxygen difference, and increased fluid in the tracheo-bronchial tree(3). Increasing pulmonary oedema may lead to a fatal outcome.

CASE REPORTS

The 4 patients with post-perfusion lung were aged 25, 36, 20 and 31 years. The first had undergone aortic valve replacement with a Bjork-Shiley prosthesis, the second received St Jude Medical aortic and mitral valvular prostheses, the third a St Jude Medical mitral valve prosthesis and the remaining patient had a Starr-Edwards mitral valve prosthesis implanted. Symptoms had their onset a few hours after surgery. Patients one and three died of the effects of the post-perfusion lung syndrome (5 days and 36 hours post-operatively respectively) ; in the other 2 patients the symptoms had been successfully reversed by treatment, and death was due to infection in one patient and myocardial failure plus pulmonary hypertension in the other.

Histology of the lungs in these patients showed essentially similar features (less marked in the two treated cases), namely many small areas of haemorrhage, oedema, scanty hyaline membranes, engorgement of small pulmonary blood

vessels and focal atelectasis. The appearances are similar to those of shock or those seen following excessive intravenous administration of fluids. I found it almost impossible in these patients to decide how much of the observed pulmonary changes were due to later respirator therapy. Pulmonary fibrosis was not observed in my patients.

COMMENT

Baer and Osborn(4) encountered this complication in 70% of 41 patients dying after total cardiopulmonary bypass. They attributed the syndrome to overdistension of the left atrium during perfusion, anoxia, hypotension, foreign proteins or denatured blood elements. Kolff et al.(5) suggested that pulmonary damage during open-heart operations is usually due to temporary over-filling of the pulmonary vascular bed with blood, leading to capillary damage. The pulmonary lesions observed following extra-corporeal circulation are similar to those found in adult respiratory distress syndrome caused by many other mechanisms(1) and long-surviving patients may show pulmonary fibrosis(6). Others have also experienced the difficulty I encountered in trying to separate the histological changes of the post-perfusion pulmonary syndrome from those induced in the lungs by respirator therapy(6).

Barratt-Boyes et al.(7) state that the use of profound hypothermia and total circulatory arrest diminished the incidence of post-operative pulmonary complications. The implication of this is that a shorter period of bypass gives a smaller dose of whatever is the cause of the problem. Craddock et al.(8) found that during haemodialysis there was a selective loss of neutrophiles and monocytes from the systemic circulation with trapping in the lungs. Both of these cells have membrane binding sites for the complement anaphylatoxin C5a. The rabbit model of shock lung(9), which uses zymosan to activate complement, results in profound neutropenia followed by hypoxaemia, tachypnoea, and haemorrhagic pulmonary oedema.

The ultrastructural features in such animals is similar to that shown by electron microscopy of the lung after cardiopulmonary bypass(10,11).

Westaby(3) set out to determine which components of the bypass circuit may trigger the complement cascade. Nylon, polyurethrane, polyethylene, polyvinyl chloride and polycarbonate form an important part of most bubble oxygenators and cardiotomy reservoirs. He found that all materials except polycarbonate activate complement to some extent and nylon was especially potent in this regard. Westaby(3) states that complement activation does not cease with the termination of bypass. Fragments of polyvinyl chloride tubing can be released by the action of the roller pump head on the tubing and as much as 7.8 mgs of plastic may be released during the first hour of pumping(12). It is thus possible that the post-perfusion syndrome is the direct result of a systemic inflammatory response caused by exposure of blood to unphysiological surfaces. The plastic bags used to store blood may also introduce plastic into the circulation e.g., phthalate ester plasticizer has been documented as migrating into blood stored in polyvinyl chloride bags(13). Total circulatory exchange may introduce as much as 300 mgs of the plastic into the circulation. Hopefully, increased understanding of the mechanisms of production of the post-perfusion lung will lead to means of preventing or minimizing this serious complication of cardiac surgery.

F. ASSESSMENT OF PANCREATIC FIBROSIS

Professor C.J. Uys and I had each independently gained the impression that patients with heart failure and/or implanted prosthetic heart valves showed a greater degree of pancreatic fibrosis than did patients who died of other causes. The present investigation was undertaken to determine whether one's impression of there being a greater incidence of pancreatic fibrosis in patients with implanted cardiac valvular prostheses compared to routine autopsy control patients was valid. Morphometry (point-counting) of 1210 randomly selected points in the histological sections of pancreas of 112 patients with valvular prostheses and in those of 20 routine autopsy control patients yielded the following results : (i) the 112 valve replacement patients showed a mean fibrosis value of 7.0% (S.D. = 9.6) and (ii) the 20 control patients had a mean value of 4.3% (S.D.= 4.5). The t statistic for the two means showed no significant difference between these 2 groups of patients (p less than 0.15). This investigation thus failed to show an increased incidence of pancreatic fibrosis in patients with valvular heart disease.

CHAPTER 18.

OVERALL REVIEW OF THE PATHOLOGICAL FINDINGS IN PATIENTS WITH PROSTHETIC CARDIAC VALVES

CHAPTER 18.

OVERALL REVIEW OF THE PATHOLOGICAL FINDINGS IN PATIENTS WITH PROSTHETIC CARDIAC VALVES

Table 18.1 compares the cumulative survival rates and the cumulative embolism event-free rates of various heart valve prostheses implanted for 4 - 5 years (from 1976 onwards) in patients at Groote Schuur Hospital.

A. NATIVE VALVULAR DISEASES LEADING TO CARDIAC VALVE REPLACEMENT

Table 18.2 indicates the diseases of the natural cardiac valves for which the patients underwent heart valve replacement. Rheumatic fever was pre-eminent as an aetiological factor. The second commonest category was a miscellaneous group of valvular diseases including aortic incompetence due to ring dilatation (caused by syphilis, ankylosing spondylitis or aortic medionecrosis), rupture of infarcted left ventricular papillary muscle, idiopathic chordal rupture and traumatic damage to a valve. Congenital valvular disease e.g., congenital bicuspid aortic valve, persistent truncus arteriosus, congenital aortic stenosis, parachute mitral valve and common atrioventricular canal defect with cleft mitral valve , was the third commonest group leading to valve replacement. In this group the calcified congenital bicuspid aortic valve was the most frequent lesion (14 out of the 22 patients).

B. THROMBOSIS ON THE PROSTHESIS AND THROMBOEMBOLISM

The number of prosthetic thrombi in patients with mechanical and tissue valves is compared in Table 18.3. The tissue valves showed significantly fewer thrombi and in general the latter were much scantier in amount than those

observed on the mechanical prostheses. (Five patients with both mechanical and tissue valves in the same heart are excluded from Table 18.3).

TABLE 18.1 : COMPARISON OF THE CUMULATIVE SURVIVAL RATES AND THE CUMULATIVE EMBOLISM EVENT-FREE RATES OF VARIOUS HEART VALVE PROSTHESES 4 - 5 YEARS AFTER IMPLANTATION AT GROOTE SCHUUR HOSPITAL.

PROSTHESIS	CUMUL. SURVIVAL RATE (%)	STANDARD ERROR	CUMUL. EVENT-FREE RATE(%)	STANDARD ERROR
STARR-EDWARDS	68.8	5.2	57.5	7.0
LILLEHEI-KASTER	63.5	4.4	72.4	3.9
BJORK-SHILEY	72.3	3.1	82.7	0.0
St JUDE MEDICAL	79.4	2.4	81.3	3.5
HANCOCK	74.2	4.6	75.8	4.7
CARPENTIER-EDWARDS	78.3	0.0	78.6	0.0

TABLE 18.2 : AETIOLOGY OF VALVE DISEASE NECESSITATING VALVE REPLACEMENT WITH A PROSTHESIS IN 275 PATIENTS

TYPE	CONGENITAL	RHEUM.	FLOPPY	I.E.	SENILE CALCIFIC	OTHER	TOTAL
MECHANICAL	21	170	4	7	6	17	225
TISSUE	1	31	1	0	6	11	50
TOTAL	22	201	5	7	12	28	275
(%)	(8.0)	(73.1)	(1.8)	(2.6)	(4.4)	(10.2)	

RHEUM=RHEUMATIC FEVER,IE=INFECTIVE ENDOCARDITIS, SENILE CALCIFIC=AORTIC NODULAR SCLEROSIS/TRICUSPID SENILE CALCIFIC AORTIC STENOSIS,FLOPPY=MYXOMATOUS DEGENERATION.

TABLE 18.3 : NUMBER OF PROSTHESES BEARING THROMBI IN PATIENTS WITH MECHANICAL AND TISSUE VALVE PROSTHESES

PROSTHESES	No.PATIENTS WITH PR. THROMBI	INCIDENCE OF PR. THROMBI PER PT.
MECHANICAL VALVES (N=220 PATIENTS)	78	0.35*
TISSUE VALVES (N=50 PTS.)	8	0.16*
TOTAL (N=270)	86	0.32

(*p less than 0.01)
PR=PROSTHETIC

Table 18.4 gives the incidence of infarcts in the body organs of patients with various types of prosthetic heart valves and Table 18.5 indicates the number of organ infarcts per patient per 100 days post-operative survival period in the mechanical and tissue valves.

TABLE 18.4 : INCIDENCE OF ORGAN INFARCTS IN PATIENTS WITH VARIOUS TYPES OF PROSTHETIC HEART VALVES

PROSTHESIS TYPE	No. OF PATIENTS	No.INFARCTS PER PATIENT (FATAL)	No.INFARCTS PER 100 POST-OP.DAYS
UCT	98	1.6(0.2)	0.4
LILL	16	1.3(0.0)	0.3
B-S	14	0.0(0.1)	0.0
S-E	44	1.0(0.4)	0.2
SJM	29	0.9(0.0)	1.4
MIXED	24	0.7(0.1)	0.5
HANC	12	0.8(0.0)	0.6
C-E	38	0.6(0.1)	0.3

UCT=UNIVERSITY OF CAPE TOWN,LILL=LILLEHEI-KASTER, B-S=BJORK-SHILEY,S-E=STARR-EDWARDS,SJM=St JUDE MEDICAL,MIXED=MULTIPLE DIFFERENT PROSTHESES IN SAME HEART,HANC=HANCOCK,C-E=CARPENTIER-EDWARDS.

TABLE 18.5 : NUMBER OF ORGANS WITH INFARCTS PER PATIENT PER 100 DAYS POST-OPERATIVE SURVIVAL AFTER HEART VALVE REPLACEMENT

SYSTEMIC ORGANS	PTS.WITH MECHANICAL VALVES (N=220)	PTS.WITH TISSUE VALVES (N=50)
BRAIN	0.02	0.03
SPLEEN	0.02	0.03
HEART	0.01	0.06
KIDNEYS	0.02	0.05
OTHER	0.01	0.00
MEAN (S.D.)	0.02 (0.01)	0.03 (0.02)
LUNG INFARCTS	0.01	0.05

The differences between the mechanical and tissue valves are not significant with regard to infarcts in the systemic organs. The 'other' infarcts referred to in Table 18.5 include infarcts e.g., of bowel and limbs. Tissue valves showed a significantly greater number of pulmonary infarcts. If the systemic and pulmonary infarcts are combined,then the greater number of pulmonary infarcts in the tissue valve group serves to create a statistically significant difference (p less than 0.05) between the 2 combined groups.

Table 18.6 compares organ infarcts encountered in 275 patients with valvular prostheses with those recorded in 103 non-operated patients with natural valvular disease. Sixty of the control patients had predominantly mitral valvular disease and 43 had aortic valvular disease ; 87% of the controls had chronic rheumatic-type valvular deformities. Patients with superimposed infective endocarditis were excluded. There was no significant difference in the incidence of renal infarcts

between operated patients and controls. Patients with prostheses showed significantly more infarcts (Chi-square evaluation) of other organs, particularly of the brain and heart. Pulmonary infarcts were commoner in the non-operated patients, most of whom were in congestive cardiac failure.

TABLE 18.6 : ORGAN INFARCTS IN PATIENTS WITH IMPLANTED CARDIAC VALVULAR PROSTHESES AND IN NON-OPERATED CONTROLS WITH NATURAL VALVULAR DISEASE (%).

	PTS WITH PROSTHESES (N=275)	NON-OPERATED PTS (N=103)	p value
KIDNEY	69 (25%)	25 (24%)	NS
SPLEEN	59 (22%)	17 (17%)	< 0.05
BRAIN	58 (21%)	14 (14%)	< 0.001
HEART	47 (17%)	6 (6%)	< 0.001
OTHER	25 (9%)	6 (6%)	< 0.05
LUNG	23 (8%)	25 (24%)	< 0.001
MEANS	47 (17%)	15 (14%)	

C. PRINCIPAL CAUSES OF DEATH

Table 18.7 compares the principal causes of death in 275 patients with heart valve prostheses divided as to whether a mechanical or tissue valve prosthesis was present. The prosthesis-related problems and the fatal complications unrelated to the cardiac operation are detailed further in Table 18.7

TABLE 18.7 : PRINCIPAL CAUSES OF DEATH IN 275 PATIENTS WITH IMPLANTED PROSTHETIC HEART VALVES

CAUSE	MECHANICAL (N=220)	TISSUE (N=50)	TOTAL* (N=275)
ERROR PRE-OP. DIAGNOSIS	5(2.3%)	0.0	5(1.8%)
ERROR OP. TECHNIQUE	25(11.4%)	7(14.0%)	35(12.7%)
PROSTHESIS PROBLEM	89(40.5%)	9(18.0%)	98(35.6%)
POST-OP.COMPLICATIONS	46(20.9%)	5(10.0%)	52(18.9%)
UNRELATED TO CARDIAC OP.	17(7.7%)	11(22.0%)	28(10.2%)
UNKNOWN	38(17.3%)	18(36.0%)	57(20.7%)

* Includes 5 patients with mixed tissue and mechanical valves in the same heart.

TABLE 18.8 : DETAILS OF VALVE-RELATED PRINCIPAL CAUSES OF DEATH IN TWO GROUPS OF PATIENTS WITH VALVE PROSTHESES

VALVE PROBLEMS	MECHANICAL VALVES	TISSUE VALVES
a)THROMBUS-RELATED	47(21.4%)	3(6.0%)
b)INFECTION	30(13.6%)	1(2.0%)
c)DESIGN/STRUCTURE	12(5.5%)	5(10.0%)

The percentages given in Table 18.8 refer to the percentage of all the principal causes of death for which that particular listed cause was responsible. Table 18.9 compares

the incidence of prosthesis-related principal causes of death in the various types of prostheses studied. In Table 18.10 a comparison is made between the principal causes of death in patients with pivoting/tilting disc or bileaflet prostheses and those with ball valves.

Table 18.11 and Fig. 18.1 compare the early (less than 1 month post-operatively, group 1) and the late (greater than 1 month post-operatively,group 2) causes of death after cardiac valve replacement. Prosthesis-associated complications accounted for 13% of the early deaths and 61% of the late deaths. Deaths unrelated to cardiac surgery were responsible for 9.1% of the early and 11.4% of the late deaths. Thus, pre-existing or associated cardiovascular diseases (error in pre-operative diagnosis),operative complications and deaths of unknown causes caused 77.9% of the early deaths and 27.6% of the late deaths. Table 18.12 compares the incidence of prosthesis-related deaths in the present series with that of other comprehensive pathological reports in the literature. The figures given for prosthesis-related complications in the reports cited in Table 18.12 are my own, being derived from study of the reports. I made an allocation as to the principal causes of death from these published reports using the same categories that I used in my patients. In these published series early deaths were those that occurred less than 1-2 months post-operatively.

TABLE 18.9 : PRINCIPAL CAUSES OF DEATH IN 275 PATIENTS WITH VARIOUS TYPES OF PROSTHETIC HEART VALVES.

VALVE TYPE		NONPROSTHESIS-RELATED DEATHS (%)		PROSTHESIS-RELATED DEATHS (%)	
UCT	(N=98)	56	(57)	42	(43)
LILL	(N=16)	9	(56)	7	(44)
B-S	(N=14)	13	(93)	1	(7)
S-E	(N=44)	21	(48)	23	(52)
SJM	(N=29)	20	(69)	9	(31)
MIXED	(N=24)	17	(71)	7	(29)
HAN	(N=12)	10	(83)	2	(17)
C-E	(N=38)	31	(82)	7	(18)

TABLE 18.10 : PRINCIPAL CAUSES OF DEATH IN PATIENTS WITH BALL-VALVES (STARR-EDWARDS) AND IN THOSE WITH PIVOTING/ TILTING DISC (LILLEHEI-KASTER,BJORK-SHILEY) OR BILEAFLET (St JUDE MEDICAL) VALVES

	BALL-VALVES	DISC/ BILEAFLET
ERROR PRE-OP.DIAGNOSIS	2.4%	5.7%
ERROR OP.TECHNIQUE	4.8%	17.0%
VALVE PROBLEMS	53.6%	34.0%
POST-OP.COMPLICATIONS	17.0%	15.0%
UNRELATED TO CARDIAC OP.	9.8%	9.4%
UNKNOWN	12.4%	18.9%

TABLE 18.11 : EARLY (GROUP 1) AND LATE (GROUP 2) CAUSES OF DEATH AFTER CARDIAC VALVE REPLACEMENT

	GROUP 1(%)	GROUP 2(%)
ERROR PRE-OP. DIAGNOSIS	4 (2.8)	1 (0.8)
ERROR IN OP. TECHNIQUE		
ANAESTHETIC	9 (6.3)	3 (2.3)
PROSTHESIS DEHISCENCE/DISPROPORTION	8 (5.6)	4 (3.0)
PUMP/STONE HEART	7 (4.9)	1 (0.8)
OTHER	2 (1.4)	1 (0.8)
INHERENT PROSTHETIC PROBLEMS		
THROMBOSIS	10 (7.0)	40 (30.3)
INFECTION	7 (4.9)	24 (18.2)
DESIGN/STRUCTURE	1 (0.7)	16 (12.1)
POST-OP. COMPLICATIONS		
GENERAL	31 (21.7)	17 (12.9)
UNIQUE TO CARDIAC SURGERY	4 (2.8)	0
UNRELATED TO CARDIAC OPERATION	13 (9.1)	15 (11.4)
UNKNOWN CAUSE	47 (32.9)	10 (7.6)
TOTALS	143	132

TABLE 18.12 : INCIDENCE OF EARLY AND LATE PROSTHESIS-RELATED CAUSES OF DEATH AFTER CARDIAC VALVE REPLACEMENT

AUTHORS(REF)	VALVE(No.PTS)	EARLY(%)	LATE(%)
ROBERTS&MORROW (143)	S-E (20)	--	25
ditto (144)	S-E (64)	48	30
ditto (145)	S-E (98)	9	30
STARR et al. (146)	S-E (32)	--	44
HERR et al. (147)	S-E (53)	15	64
STARR (148)	S-E (87)	--	58
COLAPINTO & SILVER (149)	S-E,B-S (99)	10	--
ROBERTS et al. (150)	S-E(228)	10	54
JOASSIN&EDWARDS(151)	S-E (93)	8	--
ditto (152)	S-E (36)	--	36
HENZE et al. (153)	B-S (20)	13	25
FISHBEIN et al.(154)	HUFN(20)	57	92
ditto (155)	HAN (20)	7	33
BARNHORSTet al.(156)	S-E(231)	8	35
ROBERTS&HAMMER (6)	B-S (46)	9	62
SCHOEN et al. (157)	MIXED(279)	6	47
PRESENT SERIES	MIXED(275)	13	61

S-E=STARR-EDWARDS,B-S=BJORK-SHILEY,HUF=HUFNAGEL,
HAN=HANCOCK,MIXED=VARIOUS TYPES OF PROSTHESES.

The means of the incidences of prosthesis-related causes of death in early and late survivors listed in Table 18.12, (my patients excluded), were as follows : early deaths, 16.7% (S.D.=17.0) and late deaths,45.4% (S.D.=19.0). If the poorly durable Hufnagel trileaflet prosthesis(154) is excluded, then the means are 13.0% (S.D.=11.9) and 41.8% (S.D.=14.0) respectively. The longest follow-up period in the patients with the Hufnagel prosthesis was 58 months, so the high late

mortality rate is not simply due to an unusually prolonged follow-up period. It should be noted that the simple percentage method lacks the important meaning afforded by including the length of follow-up(158). A shorter follow-up time tends to generate a lower mortality or late complication percentage than does a longer period of post-operative evaluation. Unfortunately, the papers cited in Table 18.12 do not indicate follow-up periods in patient-years. In the present series the 275 autopsy patients with implanted heart valves had a total follow-up period of 684.1 patient years (Table 18.13).

TABLE 18.13 : PATIENT-YEAR SURVIVAL AFTER CARDIAC VALVE REPLACEMENT IN 275 AUTOPSY PATIENTS.

PROSTHESIS	PATIENT-YEAR SURVIVAL
UCT	565.5
S-E	53.1
LILL	17.8
C-E	26.3
HAN	2.6
B-S	3.6
SJM	5.3
MIXED	9.9
TOTAL	684.1

Figure 18.1 : Early and late causes of death after cardiac valve replacement, 1962 to 1982.

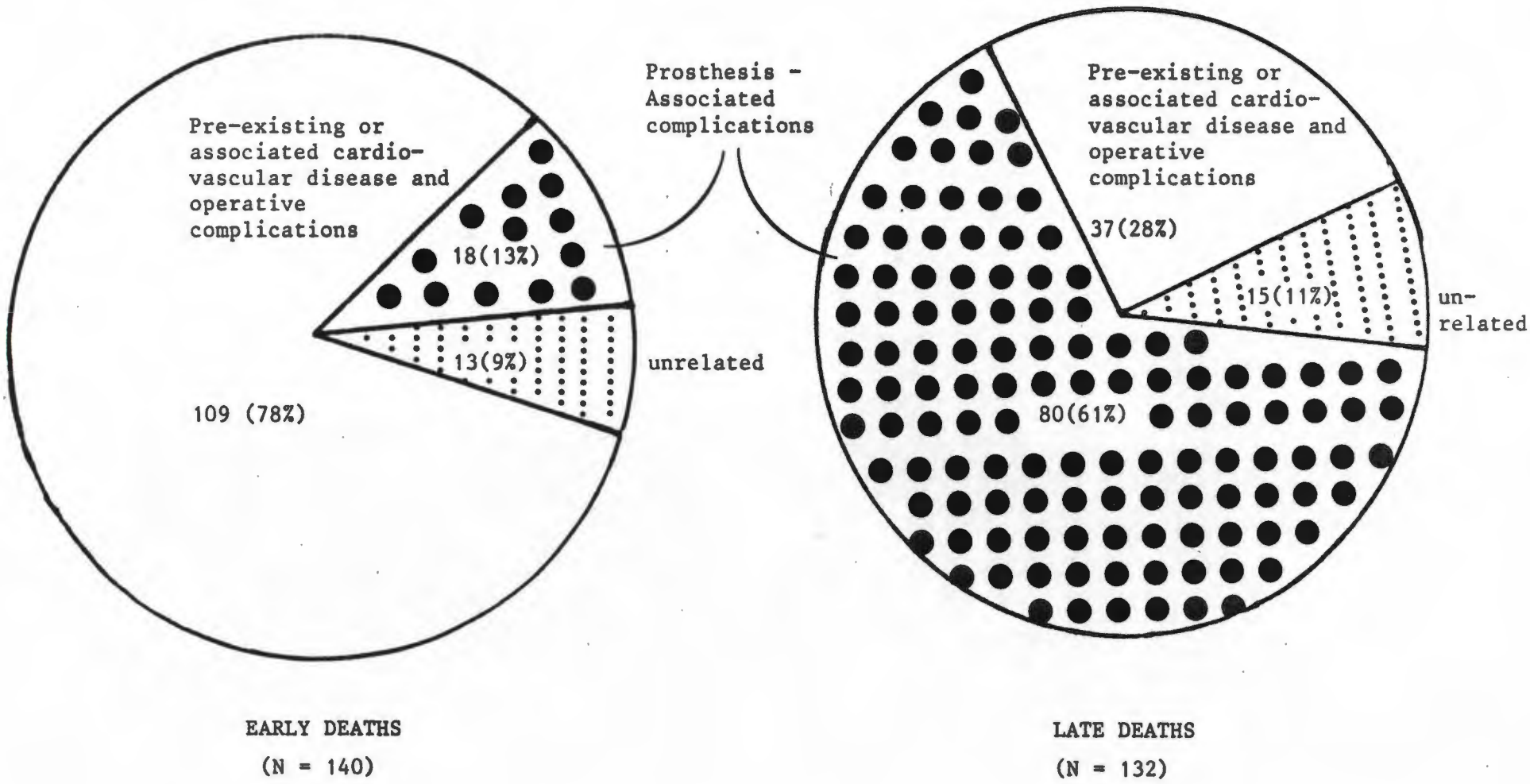

TABLE 18.14 : NON-FATAL ASSOCIATED CONDITIONS/DISEASES IN 275 PATIENTS WITH IMPLANTED CARDIAC VALVULAR PROSTHESES

CONDITION	No. OF PTS.
UNCORRECTED VALVULAR DISEASE	23
MISCELLANEOUS	22
SILICONE EMBOLI	16
LUNG DISEASE (T.B.=2)	16
75%+ CORONARY ARTERY NARROWING	14
POOR ANTICOAGULANT CONTROL	10
LESIONS OF CONDUCTING TISSUE	9
RENAL PARENCHYMAL DISEASE	
ACUTE TUBULAR NECROSIS	4
GLOMERULONEPHRITIS	2
PEPTIC ULCERATION	6
PROSTHETIC DEHISCENCE	5
WOUND INFECTION	5
SYMPTOMATIC HAEMOLYSIS	4
MALIGNANCY	3
SEVERE DIGITALIS TOXICITY	3

Table 18.4 summarizes the non-fatal associated conditions encountered in the 275 patients with implanted cardiac valvular prostheses. Uncorrected valvular disease was the commonest associated abnormality, followed by the miscellaneous group. The latter included such isolated conditions as mediastinal emphysema, extra-dural abscess, acute pancreatitis, aortic dissection, subaortic stenosis due to a mitral prosthesis, etc. Widespread silicone embolism was

a feature of the earlier autopsies prior to the use of more efficient filters during cardiopulmonary bypass. Fourteen patients had significant coronary arterial atherosclerotic narrowing, but death had been attributed to some other cause. Poor anticoagulant control was mainly reflected as bleeding into non-vital organs in this group. Three patients were found to have an incidental malignancy at autopsy ; jejunal carcinoid tumour in one patient, and lung cancer and endometrial carcinoma respectively in the other two patients.

DISCUSSION

Few studies have analysed the autopsy determined causes of death in a large group of patients with implanted prosthetic heart valves. This investigation is an analysis of a large group of patients from a single institution, who underwent cardiac valve replacement and ultimately, autopsy. The range of prostheses studied in this work reflects the ongoing quest for the perfect artificial heart valve, which will have properties equal to, or nearly approaching that of natural human heart valves. The wide variety of heart valve substitutes presently commercially available indicates that this goal is still some distance away.

It is apparent that there is a great potential for the prevention of acquired valvular heart disease in Cape Town, where there is still a high incidence of rheumatic fever. As I have shown in Chapter 3, the rate of mitral stenosis at autopsy has not diminished over the 30-year period 1950-1979. Since improvements have occurred in the socio-economic status of our community over this time period, the chronic rheumatic heart disease morbidity and mortality we are still witnessing may be a legacy of the past. Once a valve has been damaged by rheumatic fever, the structural alterations may become a self-perpetuating process due to repeated thrombus deposition and organization. Precedents for abnormal valves undergoing

progressive calcification and fibrosis are well known, as when bicuspid aortic valves develop stenosis(1). Further improvements in the socio-economic and in the general medical care of the poorer members of our community are still necessary. Hopefully, further improvements in the socio-economic status of the disadvantaged members of our population will result in the same low incidence of rheumatic fever that is a feature of the developed nations of Western Europe(1) and North America(2-4). In the present study 73% of the implanted heart valves were replaced because of chronic rheumatic heart disease (see Chapter 3 and Table 18.2 of the present Chapter). Only about 1 in 10 of such hearts showed Aschoff bodies at the time of valve surgery or at subsequent autopsy. This study confirms that rheumatic fever seldom causes isolated aortic valve stenosis. Since valve surgery is only palliative, prevention of rheumatic fever is the optimal goal.

As specific comments have already been made after each particular type of valve prosthesis studied, I shall limit the present discussion to a broad overview of the obtained results. This study confirms the lower thrombogenicity (Table 18.3) of tissue valves (despite the absence of long-term anticoagulant therapy), as compared to mechanical valves(5,6). However, the incidence of organ infarcts (Tables 18.4 and 18.5) did not differ significantly between the two groups, if the slightly greater number of pulmonary infarcts observed in the tissue valves is excluded. Patients with Starr-Edwards valve prostheses showed the greatest number of fatal thromboembolic infarcts per patient (Table 18.4).

Next, I should like to discuss the principal causes of death in the 275 patients with prosthetic valves, the identification of which was the major object of this study. It should be noted that 15 patients who form part of this work are excluded from this final analysis. Firstly, the 9 patients who received valved conduit tube grafts are not strictly analogous to the other 275 patients who underwent orthotopic

replacement of their cardiac valves and the tube conduits pose special problems of their own. Secondly, the 2 patients who died with formaldehyde-treated, locally manufactured, porcine aortic valve bioprostheses were excluded due to inadequate information regarding the extra-cardiac autopsy findings. The latter valves were never made commercially available. Other patients who are excluded from this final analysis include a solitary patient with an autologous fascia lata mitral valve prosthesis, together with the 3 patients with Ionescu-Shiley prostheses, all of which had been implanted at another hospital.

Prosthesis-related problems (e.g., thrombosis, infection of the prosthesis, or design/structural problems) comprised the biggest single principal cause of death (36%) in all patients with valve prostheses (see Table 18.7). This was followed in descending order of frequency by unknown causes, post-operative complications, errors in operative technique, diseases unrelated to the cardiac operation, and errors in pre-operative diagnosis, which included unrecognized associated significant valvular disease. Separation of the principal causes of death in the patients according to whether a mechanical or a tissue valve had been implanted left one with 270 patients, once the 5 patients with both tissue and mechanical prostheses in the same heart had been excluded.

The commonest principal cause of death in the mechanical prosthesis group (N=220) was prosthesis-related problems, whereas in the tissue valve group (N=50) this cause ranked third in order of frequency (after unknown causes and diseases unrelated to valve surgery). In the mechanical valve group post-operative complications were the second commonest cause of death. There was an equal incidence of deaths attributable to errors in pre-operative diagnosis. Analysis of the valve-related principal causes of death (Table 18.8) shows that thrombosis and infection were more important in the mechanical group, whereas structural failure was more common in the tissue valves. When the various types of prostheses are

compared with one another with regard to prosthesis-related principal causes of death (Table 18.9), it is apparent that the University of Cape Town, the Lillehei-Kaster and the Starr-Edwards valve prostheses gave the worst results, whilst the Bjork-Shiley, Carpentier-Edwards, Hancock and St Jude Medical valve prostheses (in that order) showed fewer prosthesis-related fatal complications.

Surprisingly, patients with mixed prostheses in the same heart showed only a 29% prosthesis-related fatal complication rate. Valve-related fatal complications were more frequently encountered with the Starr-Edwards ball-valves than with the pivoting/tilting disc or bileaflet prostheses (Table 18.10), viz. 54% versus 34%. There was a higher incidence of deaths due to errors in operative technique and death due to unknown causes in the nonball-valve group. Roberts and Hammer(6) noted a similar difference in "prosthesis-related" deaths between a group of patients with ball-valves and another group with tilting/pivoting disc valves, which they ascribed to the higher incidence of disproportion with the ball-valves. In my patients with Starr-Edwards ball-valve prostheses disproportion was noted as a principal cause of death in only one patient, whereas thrombosis on the prosthesis appeared to be the major problem. Such thrombosis, often associated with thromboembolism, was the principal cause of death in 16 out of 44 patients. The lower rate of disproportion in our patients with ball-valves may be related to the fact that these valves were inserted at a later time in most of our patients, by which time our surgeons had been alerted to this problem by the experience of others. Subjective observer error cannot be excluded as a factor either.

When all of the patients with prostheses (both mechanical and tissue valves) are separated into early or late survivors, with 30 days postoperative survival as the cut-off point (Table 18.11), prosthesis-related fatal complications were seen in 12.6% of the early survivors and in 60.6% of the late survivors. Prosthetic thrombosis and its related complications

was encountered more often as a principal cause of death in the late survivors (30.3%) than in the early survivors (7.0%), and so too were infection and problems related to prosthetic design or structure. Deaths due to unknown causes were commoner in patients who died less than 30 days post-operatively.

Amongst the vast current clinical literature, there are numerous reports (only some of which are cited here) detailing the in vitro(7-12), experimental testing(13-17), clinical(18-52) and haemodynamic(53-60) features of implanted heart valve substitutes, and specific complications of cardiac valve replacement e.g., haemolysis(see references 1-54 of Chapter 17, part B), thromboembolism(61-97), infection(see references 1-128 of Chapter 17, part D) and the durability of mechanical(98-113) and tissue valves(114-135). However, there are relatively few reports which primarily address the pathology of patient-prosthesis interactions. Even amongst such predominantly pathological reports on patients with implanted valve prostheses, many consist of general reviews (136-142) in which no specific data regarding autopsied patients are given. Other authors give data regarding specific complications (e.g.,myocardial necrosis), but do not indicate the major factors leading to the death of their patients(136).

I was able to find only 16 papers(6,143-157) in which a detailed description was given of the principal causes of death (based on both clinical and autopsy findings) of patients with cardiac valve prostheses, (see Table 18.12). The majority of these deal with patients with Starr-Edwards ball-valves. The longest follow-up period in the patients with an implanted Hufnagel prosthesis was 58 months, so their high late mortality rate is not simply due to an unusually long follow-up period. It should be noted that the simple percentage method lacks the important meaning afforded by including the length of follow-up (158). A shorter follow-up time tends to generate a lower mortality or late complication

percentage than does a longer period of post-operative evaluation. Unfortunately, the papers cited in Table 18.12 do not indicate follow-up periods in patient-years. My 275 autopsy patients with implanted heart valves had a total follow-up period of 684.1 years.

The series which most closely approximates my own (mixed types of valve prostheses) is that of Schoen et al.(157). Six percent of their early deaths were prosthesis-related (compared to 13% of my patients) and 47% of their late deaths (compared to 61% of my patients) were due to prosthesis-related complications. These findings are consistent with the general trend found in the other detailed pathological reports cited in Table 18.12, with the exception of report of Fishbein et al.(154) which reflects the poor durability of the Hufnagel trileaflet prosthesis and that of Roberts and Morrow(144) which had an unusually high rate of early prosthesis-related complications.

CHAPTER 19 : CONCLUSIONS

CHAPTER 19 : CONCLUSIONS

1. There is a high incidence of rheumatic heart disease at autopsy in Cape Town. Only time will tell whether this is still a late legacy of a previously high incidence of acute rheumatic fever or whether further improvements in the socio-economic status of our community are still needed. The latter is more likely.

2. For optimal pathological examination and interpretation of surgically excised diseased cardiac valves the pathologist should be given adequate data regarding the pre-operative history of the patient, the appearance of the valve at operation and the clinically suspected aetiology of the valvular disease.

3. Muscle-associated granulomas and lymphocytic aggregates may be confused with true Aschoff bodies.

4. The wide variety of heart valve prostheses, which have been implanted in patients at Groote Schuur Hospital reflects the ongoing, as yet unfulfilled, search for the ideal cardiac valve substitute.

5. Tissue valves showed a lower incidence of thrombosis on the valve prosthesis compared to mechanical valves, despite the fact that no long-term anticoagulation was given to patients with tissue valves. However, there was no significant difference at autopsy between these 2 groups of patients with regard to the number of systemic organs showing infarcts. Patients with implanted valvular prostheses did not show a greater incidence of organ infarcts than did non-operated controls with (mainly rheumatic) valvular disease. This emphasizes the fact that rheumatic fever is a thromboembolic disease in its own right(1).

6. Tissue valves are not suitable for use in children and young persons due to the problem of prosthetic cuspidal calcification.

7. Prosthesis-related complications comprised the commonest principal cause of death in patients with mechanical prostheses, whereas in those with tissue valves it was third in frequency (after unknown causes and deaths unrelated to the cardiac operation). Prosthesis-related fatal complications had the highest incidence in patients with Lillehei-Kaster, University of Cape Town and Starr-Edwards prostheses, whilst those with Bjork-Shiley prostheses showed the lowest incidence. Thrombosis or infection of the valve prosthesis were more commonly encountered amongst the mechanical prosthesis group, whereas structural failure of the valve prosthesis was more often encountered in the tissue valve group of patients. Prosthesis-related fatal complications were more frequent in the late survivors compared to those dying within one month after surgery. Within the mechanical prosthesis group of patients, prosthesis-related fatal complications were more often encountered in patients with (Starr-Edwards) ball-valves than in those with tilting disc/bileaflet prostheses.

8. Patients dying of myocardial failure had heavier hearts than those who died of other causes. No significant difference in myocardial necrosis scores was found between the following groups of patients : operated versus control patients with valvular disease ; patients who did and did not receive cold cardioplegia during bypass ; and those who received intermittent versus continous coronary arterial perfusion during bypass. Total groups of patients and controls showed equal amounts of myocardial fibrosis.

9. Experimental in vivo evaluation of the Mitroflow bovine pericardial heart valve yielded less satisfactory results than were obtained with a small number of control Ionescu-Shiley prosthetic valves, which the Mitroflow valve aims to replace.

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REFERENCE FOR CHAPTER 19 : CONCLUSIONS

1.Abernathy, W.S., Willis, P.W. III : Thromboembolic complications of rheumatic heart disease. Cardiovasc. Clin. 1973 ; 5 : 131.

LIST OF ILLUSTRATIONS

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TYPES OF CARDIAC VALVULAR PROSTHESES IMPLANTED IN 290 AUTOPSIED PATIENTS

VALVE TYPE	SITE IMPLANTED	NO. OF PATIENTS
MECHANICAL		
UNIVERSITY OF CAPE TOWN	AORTIC	41
ditto	MITRAL	36
ditto	TRICUSPID	2
ditto	MULTIPLE	19
LILLEHEI-KASTER	AORTIC	9
ditto	MITRAL	7
BJORK-SHILEY	AORTIC	12
ditto	MITRAL	1
ditto	MULTIPLE	1
STARR-EDWARDS	AORTIC	7
ditto	MITRAL	34
ditto	MULTIPLE	3
St JUDE MEDICAL	AORTIC	10
ditto	MITRAL	9
ditto	TRICUSPID	1
ditto	MULTIPLE	9
TISSUE		
FORMALIN-TREATED XENOGRAFT	MITRAL	2
HANCOCK	AORTIC	1
ditto	MITRAL	8
ditto	MULTIPLE	3
CARPENTIER-EDWARDS	AORTIC	15
ditto	MITRAL	16
ditto	MULTIPLE	7
FASCIA LATA VALVE	MITRAL	1
IONESCU-SHILEY	MITRAL	3
MIXED PROSTHESES	MULTIPLE	24
VALVED CONDUITS	___	9

TOTAL = 290

DATA ON CONTROL PATIENTS

CONDITION TESTED	NO. OF CONTROLS	AGE IN YRS MEAN,(S.D.)	FEMALES (%)
ORGAN INFARCTS	103	46 (14.3)	49
CONDUCTION TISSUE	14	51 (13.6)	55
HAEMOSIDEROSIS			
VALVE DISEASE	32	44 (18.5)	52
ROUTINE AUTOPSY	21	49 (16.1)	51
SMALL CORON. ARTS.			
ACTIVE RHEUMATIC F.	13	36 (17.4)	58
HEALED RHEUMATIC F.	26	47 (15.8)	53
MYOCARDIUM	85	38 (15.0)	61
PANCREAS	25	54 (14.2)	55